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THE EFFECT ON ENDOGENOUS THYROID ACTIVITY OF FEEDING DESICCATED THYROID TO NORMAL HUMAN SUBJECTS*

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IT HAS been known for many years that a reciprocal relation appears to exist between the levels of circulating thyroxin and thyrotrophin in the vertebrate species so far investigated. Until recently, however, direct tests of thyroid activity in man have not been feasible. Within the last few years, radioactive iodine has provided a new method for the study of thyroid function, permitting observations that would otherwise be impossible. Using shielded G–M counters, it is possible to follow directly the accumulation of radioiodine in the thyroid gland. Studies in several clinics have indicated that this method is an accurate index of thyroid function.

In view of the widespread therapeutic use of thyroid medication, it was of interest to determine whether the administration of physiologic amounts of the hormone to man would produce the same compensatory depression of the thyroid gland as that observed in laboratory animals. Previous investigators, using other measures of thyroid function, have observed that the thyroid gland is depressed by thyroid feeding. Farquharson and Squires[1] found that the administration of moderate doses of desiccated thyroid to apparently euthyroid "hypometabolic" subjects produced no appreciable elevation of the initially low basal metabolic rate. On the contrary, when thyroid medication was stopped, the basal metabolic rate fell rapidly below the pretreatment level and remained depressed for several weeks before gradually rising to the initial level. Riggs and his co-workers[2] administered gradually increasing amounts of thyroid up to 20 to 25 gr. daily to euthyroid subjects. It was found that both the basal metabolic rate and the serum-precipitable iodine remained relatively constant until daily doses in excess of 3 to 5 gr. were given, when both indices of thyroid activity began to rise concomitantly. When the administration of thyroid was abruptly stopped, the basal metabolic rate and serum-precipitable iodine fell abruptly, but transiently, to abnormally low levels, indicating an inhibition of endogenous hormone production and a delayed return to normal thyroid function.

The present investigation was designed primarily to determine how rapidly depression of the normal human thyroid gland occurs after the institution of daily physiologic doses of thyroid hormone, how much hormone is required daily to produce complete depression of the thyroid and how rapidly recovery of thyroid activity occurs after the cessation of therapy.

MATERIALS AND METHODS

Forty-seven normal human volunteers, consisting chiefly of laboratory technicians, physicians and nurses, were employed. They were between 17 and 67 years of age, and all but three were women. All were clinically euthyroid so far as could be determined, although basal metabolic rates were obtained in only a few instances. About one fourth of the subjects had taken thyroid previously at one time or another; three had stopped the hormone only a few weeks before beginning the experiment. Four had been taking 3 or more grains daily for several years, the initial study of all but one of these being made while they were still taking the hormone.

Studies with radioactive iodine were made with a modification of the technic devised by Astwood and Stanley.[3] The isotope with an eight-day half-life, I^{131}, was used. Following the administration of a 50-microcurie tracer dose of I^{131}, serial counts were made over the thyroid gland by means of an externally placed shielded gamma counter. Since the 24-hour uptake had been found to be as reliable as any index of thyroid function determined by means of I^{131} only this measurement was used.

The I^{131} was obtained from Oak Ridge; the standardization made at that laboratory before shipment was accepted. An amount of radioactive iodine approximating 50 microcuries was pipetted into a 50-cc. Erlenmeyer flask and diluted with 15 to 20 ml. of tap water. The flask was then placed in front of the shielded gamma counter, and the absolute quantity of radioactivity determined. The distance of the flask from the end of the gamma tube was measured by a ruled steel slide, at the edge of the shielding, which was connected to a thin

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brass pointer centered in the aperture of the shield. In subsequently determining the radioactivity present in the thyroid gland, the counter was arranged so that this pointer just touched the skin over the center of the subject's thyroid gland. The distance from the flask to the end of the gamma tube was kept the same as the distance from the thyroid gland to the end of the tube, and was 55 cm. in all instances. The percentage of the administered dose in the thyroid gland at any given time could thus be determined by simple calculation. Although the count was probably increased somewhat by back scatter in the tissues of the neck, this remained constant for any one subject, so it did not introduce an error in the calculation of changes during different periods of observation.

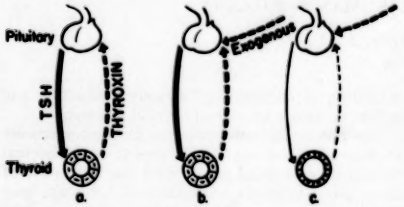

FIGURE 1. A. *Schematic Presentation of the Normal Thyroid-Pituitary Relation.*

Thyrotrophin stimulates the thyroid gland to produce thyroxin, which in turn, while catalyzing general cellular metabolism, acts on the pituitary gland to inhibit the further production of thyrotrophin. A finely adjusted balance is thus achieved, maintaining reciprocity between the circulating levels of thyrotrophin and thyroxin. The pituitary gland acts as a thermostat, controlling the level of body metabolism through its action on the thyroid gland.

B. *If, however, exogenous thyroid hormone is administered, either as thyroid extract or thyroxin, the level of circulating thyroxin becomes too high.*

C. *Marked inhibition of pituitary thyrotrophin secretion is produced and maintained by this exogenous hormone, and if the quantity is equivalent to that produced endogenously complete depression of the thyroid gland may be produced. In this way a stable euthyroid level of circulating thyroid hormone may be maintained in spite of the administration of desiccated thyroid so long as toxic amounts are not given.*

The radioiodine was administered by mouth. The subject was not required to be in the fasting state before drinking the iodine. The flask was rinsed once with 15 to 20 ml. of tap water, which the subject then drank to ensure removal of all radioactivity from the flask and to wash the I^{131} into the stomach from the mouth and pharynx. A single rinsing was found sufficient to remove 99 per cent of the radioactivity from the flask. The background was considered equivalent to the radioactivity found when the counter was placed over the lower thigh, an area roughly the size of the neck.

The normal limits of the amount of radioactive iodine present in the thyroid gland at the end of 24 hours have been set arbitrarily between 10 and 50 per cent of the administered dose. Although normal subjects have occasionally been found to have 24-hour uptakes higher than 50 per cent (five such persons were found in this investigation), the uptake is rarely less than 15 per cent, unless true hypothyroidism exists. Conversely, patients with myxedema almost invariably have uptakes below 10 per cent. In these studies, "marked" depression of the thyroid gland was therefore considered to exist if the 24-hour uptake was less than 10 per cent. Thus all subjects presumed to have marked thyroid depression had thyroid function equivalent to that seen in myxedema, as determined by radioiodine studies.

In the repeated determinations of thyroid function in the same subject several days apart, the amount of radioactivity present in the gland immediately before the administration of the succeeding dose was first determined; it was then subtracted from all following determinations during the next day or two, correction always being made for decay. It was assumed in these calculations that the I^{131}, once bound in the gland, did not significantly decrease during short periods.

U.S.P. desiccated thyroid (Burroughs Wellcome & Co.) was used in all experiments. The tablets were usually taken by the subject on arising in the morning, although if several were taken daily some subjects preferred to space them out during the day.

RESULTS

Rapidity of Depression of the Thyroid Gland after Institution of Daily Physiologic Doses of Exogenous Thyroid Hormone

Twelve subjects were given 3 grains of thyroid daily after control uptake studies had been made (Fig. 2). Repeated determinations of thyroid activity were made at intervals of a few days. In all subjects susceptible to this dosage, marked depression was produced in approximately one week. One subject had only a partial thyroid depression on this dosage, the 24-hour uptake falling from 43 per cent in the control period to 21 per cent. When given 6 grains of thyroid daily for 2 weeks she showed a further fall to 15 per cent, but it was only after a course of 9 grains daily for 10 days that complete depression (7 per cent) was accomplished. Increasing the dose to 12 grains daily for 2 weeks did not produce any further diminution of thyroid function.

Daily Amount of Hormone Required to Produce Marked Depression of the Thyroid

Since marked depression had been produced in all susceptible subjects within one week, it was considered that adequate time would elapse for equilibrium to be reached between the circulating thy-

roxin level and pituitary thyrotrophin production if the subjects received a given daily dose for three-week periods. After control studies were made, 25 subjects were given 1 grain of thyroid daily for 3

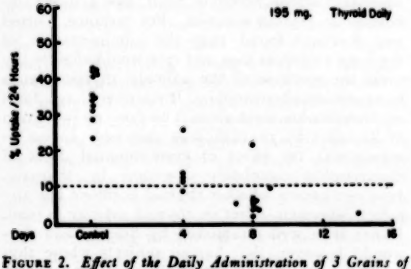

FIGURE 2. *Effect of the Daily Administration of 3 Grains of Desiccated Thyroid on the I^{131} Uptake of the Normal Thyroid Gland.*

Each dot represents a single subject. It can be seen that in all but one subject the thyroid showed marked depression within 8 days. The one subject whose uptake was reduced to only 23 per cent was subsequently found to require 9 grains daily for marked depression.

weeks. This was immediately followed by successive courses of 2, 3, then 4 grains daily, each for three-week periods. At the end of each period, studies with I^{131} were repeated. It can be seen in

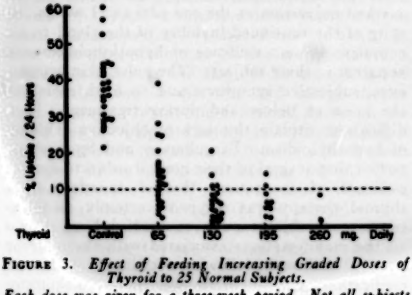

FIGURE 3. *Effect of Feeding Increasing Graded Doses of Thyroid to 25 Normal Subjects.*

Each dose was given for a three-week period. Not all subjects showing marked depression were continued on the larger doses, but all others were. Thus, one third of the subjects showed marked depression by 1 grain of thyroid daily, and all showed marked depression by 4 grains.

Figure 3 that marked thyroid depression was obtained in one third of the subjects by administration of 1 grain of desiccated thyroid daily; that all but 4 showed marked depression on ingestion of 2 grains; that only 2 showed a 24-hour uptake higher than 10 per cent while taking 3 grains and that all showed marked depression on a course of 4 grains daily. Not all subjects who showed marked depression on the lower dosages were continued at higher levels of hormone administration, but all others were. Thus those not showing marked depression at any given level represent the entire initial group.

Rapidity of Recovery of Thyroid Activity after Cessation of Therapy

In this phase of the investigation, subjects were studied during a control period without therapy, while showing marked depression, and at intervals

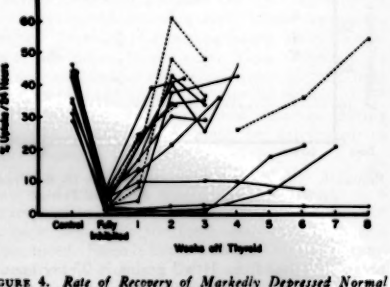

FIGURE 4. *Rate of Recovery of Markedly Depressed Normal Thyroid Glands.*

The solid lines represent subjects who had taken thyroid 1 to 6 weeks; the broken lines represent subjects who had taken thyroid 4 to 15 years. The subject still showing marked depression 8 weeks after the cessation of therapy had had no recovery of thyroid function at 11 weeks. Only subjects studied during the acute administration of thyroid had control determinations of I^{131} uptake. It can be noted that no essential difference existed between the rate of recovery of acutely and chronically depressed thyroid glands.

of one to three weeks thereafter (Fig. 4). Four apparently euthyroid subjects who had been taking thyroid for 4 to 15 years were also studied. No significant difference could be seen between the rate of recovery of glands depressed only a few days and that of those depressed for several years. In most instances complete recovery had occurred within two weeks after the cessation of therapy, although 4 subjects still showed marked depression at three weeks, 2 at the end of six weeks, and one at eleven weeks following cessation of therapy.

Effect of Administering the Equivalent of 3 Grains of Thyroid Daily as Potassium Iodide

After the control studies were made, 5 normal subjects were given 380 microgm. of iodine daily as

a solution of potassium iodide. After 8 days of this treatment, radioactive iodine studies were repeated (Fig. 5). It can be seen that although the uptakes showed a slight tendency to decrease, this tendency was minimal. In fact, 2 of the subjects showed a slight increase in the 24-hour uptake on this regimen.

Discussion

Judging by the data of these experiments, it seems that the administration of an adequate daily physiologic dose of thyroid hormone will markedly depress the endogenous thyroid function of normal human subjects within one week. The amount of hormone required to produce marked thyroid depression varied from 1 to 3 grains in 93 per cent of those studied. An occasional subject may require considerably larger doses, however. The 24-hour uptake of one subject did not fall below 10 per cent until she was taking 9 grains daily.

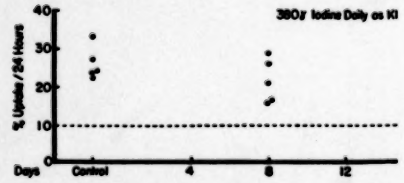

FIGURE 5. *Five Normal Subjects Given Daily the Oral Iodine Equivalent of 3 gr. of U.S.P. Desiccated Thyroid.*

It is probable that the amount of hormone required to produce marked depression of the thyroid gland is an indication of the amount of hormone secreted endogenously to keep the organism functioning at a euthyroid level. Thyrotrophin production will be reduced to a minimum when the level of circulating thyroxin can be maintained entirely by exogenously supplied hormone. It is not surprising that the 24-hour uptake did not fall to near zero in all glands markedly depressed. Considerable variation exists in the thyroid function of completely hypophysectomized animals, as measured by the concentration of radioactive iodine, although in all instances thyroid function is markedly diminished when compared to that of intact animals. Similar variation seemed to exist in the subjects studied in this investigation. Although some individuals had 24-hour uptakes of 2 per cent or less while taking 1 or 2 grains daily, others had uptakes of 6 or 7 per cent while taking only 1 grain, and no further reduction was produced by increasing the dose of thyroid. The subject who required 9 grains to depress the uptake to 7 per cent also had no further thyroid depression when taking 12 grains daily.

Although there is general agreement among most investigators that the chief determinant of thyroid activity in the normal animal is the level of circulating thyrotrophin, there is some question whether thyroid hormone itself has a direct influence on thyroid function. For instance, Cortell and Rawson[4] found that the administration of thyroxin to guinea pigs and rats would slightly depress the response of the animals' thyroid glands to exogenous thyrotrophin. If relatively large doses of thyrotrophin were given, however, no inhibition of its effect by thyroxin was observed. In no instance was the effect of even minimal doses of thyrotrophin completely overcome by thyroxin. It is not known whether thyroid hormone has any direct depressant effect on thyroid activity in man. It has been well established by Stanley and Astwood,[5] however, that human subjects whose thyroid glands do not accumulate an appreciable amount of I^{131} while under the influence of exogenous thyroid hormone can be stimulated to normal activity within 8 hours after the administration of a single small dose of thyrotrophin. It seems reasonable to assume, in view of the evidence at present available, that at least the greater part of the decrease in endogenous thyroid activity observed during the administration of exogenous hormone in these experiments was due to an inhibition of thyrotrophin secretion by the pituitary gland.

The rapid return of the depressed thyroid gland to normal function is quite interesting. Although the majority had returned to normal within 2 weeks after the cessation of therapy, some still showed marked depression at the end of 6 to 11 weeks. In spite of the continued inability of the gland to accumulate I^{131}, no evidence of hypothyroidism was apparent in these subjects. The pulse, skin, weight, eyes, subjective symptoms and so forth remained the same as before and during treatment. It is difficult to explain this lack of objective evidence of hypothyroidism. Farquharson and Squires[1] reported that several of their normal subjects showed evidence of inadequate thyroid function when thyroid therapy was stopped; certainly all myxedematous subjects we have studied have shown all the manifestations associated with that disease within 2 to 4 weeks following withdrawal of thyroid medication. One might suggest that a dichotomy exists between the synthesis and the release of thyroid hormone, and that thyroxin secretion from the large store of hormone known to be contained in the gland might have been restored more rapidly than it was formed. Such a suggestion seems unlikely, however, since thyrotrophin appears to stimulate both production and release of thyroxin with equal facility. Unfortunately, concentrations of serum-precipitable iodine were not determined, so it is not known whether the apparent lack of

thyroid function, although without clinical evidence of hypothyroidism, was associated with normal levels of circulating thyroxin.

It is interesting that subjects who had been taking desiccated thyroid for several years showed as rapid a return of thyroid function as did those subjects who had been taking the drug only a few days. This strongly indicates that chronic depression of the thyroid gland produces no permanent injury. One other interesting feature is that a "rebound" phenomenon seems concomitant with the return of the depressed thyroid glands to normal. This was especially evident in the continuously treated subjects: two had uptakes higher than 50 per cent in the first swing of recovery, which subsequently dropped below this level. Uptakes of from 50 to 75 per cent have been observed in 5 other patients after withdrawal of thyroid hormone, which they had been taking for several years, but these were not included in the present study because only a single determination of their thyroid function was made. This rebound is presumably due to a lag in the adjustment of pituitary thyrotrophin production. The depressed pituitary may be stimulated to increased secretion of thyrotrophin as the level of circulating thyroxin falls upon cessation of therapy. However, there is perhaps a certain lag before the pituitary again becomes inhibited by increased endogenous thyroid secretion, the thyroid gland thus becoming overstimulated. This same type of delayed readjustment is probably responsible for the fall in basal metabolic rate and serum-precipitable iodine seen after the withdrawal of exogenous thyroid. It is possible that the occasional case of thyrotoxicosis seen to develop upon the withdrawal of thyroid medication from euthyroid patients may be partially explained on this basis. At least one of the subjects in this study showed a definite increase in the size of the thyroid gland after withdrawal of the drug and during the return to normal of thyroid function. Although the gland was not palpable before or during the period of thyroid administration, it became 2 to 3 times enlarged during the post-treatment period. This subject was one whose gland remained depressed for several weeks after the thyroid administration was stopped, and it was only as the uptake returned to normal that thyroid enlargement became apparent.

There was some question whether the iodine contained in the thyroid administered was sufficient to increase the "iodide pool" of the body to such an extent that the accumulation of I^{131} would be depressed. This seemed unlikely for several reasons. The daily iodine requirement of man has been estimated to be roughly 100 to 200 microgm. Ten gm. of iodized salt (American) contains approximately 1 mg. of iodine, about 10 times the daily requirement. Many normal subjects we have studied have been known to consume iodized salt, yet their accumulation of I^{131} has been well within the normal range. Also, Stanley[6] found that the administration of several mgm. of iodide to normal subjects had no acute effect on the accumulation of I^{131}. Since U.S.P. desiccated thyroid contains only 0.2 per cent iodine, and the greater part of this is not present as iodide, it seemed improbable that enough iodine would be added to depress significantly the accumulation of radioactive iodine. In support of this, Riggs and his co-workers found no appreciable rise in the inorganic iodine of euthyroid subjects until thyroid in excess of 5 gr. daily was given. However, in order to test this hypothesis, 5 subjects were given 380 microgm. of potassium iodide daily for 8 days. If the uptakes before and after treatment (Fig. 5) are compared with those of subjects receiving an equivalent amount of thyroid hormone (3 gr. daily) for the same period of time, it can be seen that while all but 1 of the subjects receiving thyroid showed marked thyroid depression, *none* of the subjects receiving iodine alone showed depression below 16 per cent. Thus, although the iodine contained in the administered thyroid may have contributed slightly to the depression of I^{131} uptake, the marked depression observed during hormone administration must be attributed to other causes.

The data presented indicate that the administration of exogenous thyroid hormone results in a corresponding depression of endogenous thyroid function, whatever the mechanism by which this is produced. Since it has been found that the serum-precipitable iodine and the basal metabolic rate do not rise in normal subjects unless thyroid in excess of 3 to 5 grains daily is given, it seems reasonable to assume that a stable euthyroid level of circulating thyroxin is maintained by a depression of endogenous hormone formation equivalent to the amount administered. This stable level is probably maintained through pituitary regulation.

The administration of small doses of thyroid to normal patients for the control of obesity, menstrual disturbances, "fatigue" and so forth would thus seem to be without reason or promise of therapeutic effect, since excessive amounts would be required before any elevation of the levels of circulating thyroxin and basal metabolic rate could be produced. The doses commonly administered for these disorders are certainly below what would be considered toxic levels, and the only effect to be expected would be a compensatory depression of endogenous thyroid activity. The disappointing experiences of clinicians in their attempts to treat apparently euthyroid patients for such disorders are thus readily explained. The occasional patient who complains of symptoms of hyperthyroidism while taking only 3 to 4 grains of thyroid daily may represent those persons whose thyroid glands become markedly depressed by the exhibition of 1 gr. or less of hormone daily. Three grains would thus be

three times their daily requirement; this might possibly give rise to symptoms of overdosage.

It is of interest to consider the "increased sensitivity" of myxedematous patients to exogenous thyroid hormone. This supposition seems to have existed since the days of the first successful treatment with thyroid extract of patients with Gull's Disease. So far as the author is aware, no evidence has been published that establishes any difference in the tissue susceptibility to thyroid hormone of euthyroid subjects from that of myxedematous subjects. It is frequently stated that myxedematous patients show signs and symptoms of "toxicity" at lower dosage levels than do those with normal thyroid glands, but adequate data supporting this statement have never been presented. There is no question that small doses of hormone have a much greater effect in raising the basal metabolic rate and relieving the evidences of hypothyroidism in myxedematous than in euthyroid patients. This is readily explained by the necessity for first equaling endogenous hormone production before any elevation of the basal metabolic rate can be produced in normal subjects. Riggs and his co-workers[2] seem to be correct in assuming that the failure of the serum-precipitable iodine to rise until 3 to 5 grains of thyroid were administered daily to normal subjects was due to the necessity of first depressing endogenous thyroid activity. However, they stated that this did not adequately explain the differences between the two groups, since hypothyroid patients became "toxic" on such low doses that they could not obtain data equivalent to that on euthyroid patients who took large doses. They suggested that the thyroid gland in intact patients is capable of "breaking down" thyroid hormone, an explanation that seems unlikely in view of the evidence of Leblond and Süe[7] that the thyroid gland is incapable of concentrating organically bound iodine and that it is only when the element is available as inorganic iodide that accumulation is possible. Certainly the evidence presented by Riggs[2, 8] indicated little difference in the responses of subjects with and without thyroid glands, since the basal metabolic rate increased as much for an equivalent rise in serum-precipitable iodine in normal persons as in those with myxedema.

As gradually increasing doses of thyroid are given to patients with myxedema, there is a progressively diminishing augmentation of the basal metabolic rate as it approaches normal. Thus, 1 grain of thyroid taken daily will produce a much greater increment in the basal metabolic rate of an untreated myxedematous patient with a basal metabolic rate of −30 per cent than it will in a myxedematous patient already being treated with 1 grain daily who has a basal metabolic rate of −10 per cent. If the basal metabolic rate is plotted against the dose of thyroid given in myxedematous patients, a curve is seen that approaches a plateau as the metabolism returns to normal.[9] It seems quite possible that if this curve were extended and thyroid given in doses equivalent to the 5 to 25 gr. administered by Riggs to normal subjects, no difference would be found between subjects with and those without thyroid glands. It would be expected that much larger doses of thyroid would be required to produce an equivalent rise of the metabolic rate if the subject were near the euthyroid level before treatment was begun. Such has in fact been found to be the case in investigations of intact subjects.

Summary

The effect of exogenous thyroid hormone on the endogenous thyroid function of 47 normal human subjects has been investigated with the use of radioactive iodine. Marked depression of the subject's thyroid gland could be produced within one week by the administration of adequate daily physiologic doses of hormone. The daily amount of hormone required to produce marked thyroid depression was between 1 and 3 grains in 93 per cent of those studied, although one girl required 9 grains. After the withdrawal of therapy, thyroid function returned to normal in most subjects within two weeks, although a few subjects showed depression for six to eleven weeks. Thyroid function returned as rapidly in those subjects whose glands had been depressed by several years of thyroid medication as it did in those whose glands had been depressed for only a few days. Thus no permanent injury to the thyroid gland seems to be produced by long-continued hormone administration. It is felt that the reduction in endogenous thyroid function was brought about through a depression of pituitary thyrotrophin secretion.

It is suggested that no important difference in sensitivity to thyroid hormone exists between athyreotic and intact subjects.

I am indebted to Dr. Joseph F. Ross for the use of his laboratory during this investigation.

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NEWER ANTIBIOTICS IN THE TREATMENT OF ANTHRAX*

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WE RECENTLY reported on the use of aureomycin in the treatment of two cases of anthrax.[1] We now wish to record our experience with eight additional cases that were successfully treated with the newer antibiotics. Two patients received aureomycin; four, Chloromycetin and two, terramycin.

All but one case occurred in various departments of a factory that manufactures coat interlinings. The exception was an employee of a subsidiary plant. The source of infection was goat hair imported from India and North Africa. In all cases, the diagnosis of anthrax made by one of us (H. G.) was confirmed by smear and culture of the lesion performed by Dr. G. Sickel, pathologist of the Chester Hospital, Chester, Pennsylvania. Determinations of plasma concentrations of the antibiotic used in a given case and antibiotic sensitivity tests of the anthrax cultures isolated from these patients were performed in the laboratories of the Section of Infectious Diseases of the Hospital of the University of Pennsylvania, under the direction of one of the authors (W. P. B.).

CASE REPORTS

CASE 1. J. G., a forty-five-year-old woman, was seen on August 2, 1949. She had been well until July 29, when, while working, she noted itching in the lobe of the left ear. The next day, she scratched what appeared to be a "bite." On August 2, the itching became intense, and swelling of the lobe developed. Her temperature was 98.8°F. Examination revealed edema of the left ear lobe. On the posterior surface there was a small ulcerated papule, covered by a dry black eschar and surrounded by an area of erythema. No adenopathy was found. A diagnosis of anthrax was made, but specific therapy was not started until the next morning, when the patient seemed very apprehensive. The swelling had definitely increased, and the temperature was 98.8°F. At noon, treatment with aureomycin (500 mg. every 4 hours) was begun. On August 4, after 6 doses of the drug, the ear and the angle of the jaw were much less swollen but the pustule was unchanged. Aureomycin dosage (every 6 hours) was continued, but nausea and vomiting developed. On August 5, therapy was discontinued after the ingestion of 4.5 gm. of the drug in 54 hours. On August 6, the pustule was flat and dry. The eschar dropped off two days later, leaving a shallow ulcer. The patient returned to work on August 10; the wound was completely healed by August 12.

CASE 2. Mrs. T. P., a twenty-eight-year-old woman, noted on September 10, 1949, an itchy "pimple" on the outer surface of the right forearm. Three days later, at work, she knocked the "pimple" against a roving frame, and it bled. Thereafter, the forearm hurt and throbbed more than it itched, motion of the right axilla was painful, and the patient felt hot and developed malaise. On September 14, she was seen by us. The temperature was 99.6°F.; a blue-black papule, 12 by 16 mm., with a ring of fine vesicles and surrounded by a small zone of edema, was found on the lateral aspect of the right midforearm. A tender lymph node was palpated in the right axilla. Aureomycin, 500 mg. every 4 hours, was ordered. On September 15, the forearm was more swollen, and the pustule was surrounded by an area of erythema 5 cm. in diameter; a wide bright-red, slightly tender streak was seen along the inner surface of the arm, but the axillary adenopathy was unchanged. The patient's temperature was 98.6°F.; the white-cell count was 4800, with 77 per cent neutrophils, 21 per cent lymphocytes and 2 per cent monocytes. The sedimentation rate (Cutler method) was normal. At 6:00 p.m. the temperature was 98.6°F.; the patient felt better, except for some frequency and bladder discomfort. Lymphangitis was decreasing. On September 16, the red streaks were gone, and the edema of the forearm was lessened. The lesion was black, its vesicles were crusting and the surrounding erythema had cleared. The axillary node was the size of a walnut, and slightly tender. There was no fever. On September 17, the patient complained of frequent urination and vague discomfort in the suprapubic area, bloating and upper abdominal fullness. She was able to move the right arm freely without pain. The lymph node was no longer palpable, but slight tenderness was still present in the apex of the axilla. Aureomycin dosage was decreased to 250 mg. every 4 hours, and the 2:00 a.m. dose was omitted. The last dose of aureomycin was taken at 10:00 p.m. on September 18, after a total intake of 10.25 gm. in 100 hours. On September 19, edema of the forearm was barely noticeable. The patient returned to work on September 26, after the eschar fell off, but the ulcer did not heal completely until two weeks later.

CASE 3. A. G., a forty-one-year-old woman, was seen on November 11, 1949, because of a lesion on the medial border of the lower third of the right forearm. The patient had noted a "sore" on November 4, which was attributed to a splinter. It became worse in spite of daily applications of iodine and alcohol. Examination revealed a typical bluish-gray ulcer 5 mm. in diameter, surrounded by a ring of flat, yellowish vesicles; there was erythema of the skin over an area 5 cm. in diameter, and some swelling of the underlying soft tissues. The results of the tests of sensitivity to various antibiotics of the infecting strain of anthrax bacillus are shown in Table 1. On November 12 there was no fever; slight pain in the right axilla was present. Therapy was withheld until the 13th, when some increase in the swelling of the forearm was noted. Administration of 250 mg. of Chloromycetin every 6 hours was ordered. Plasma titrations performed 2, 4 and 6 hours after the ingestion of 250 mg. of the drug demonstrated the presence of less than 7.5 microgm. of Chloromycetin per cc. On the 14th, the edema was less and the lesion was dry and flat. No adenopathy was found. On November 15, the eschar was incised for a smear and culture, which were reported negative for anthrax. The last dose of Chloromycetin was taken at 12 noon, after a total intake of 2.25 gm. in 48 hours. The eschar was removed on November 18, leaving a shallow ulcer that healed completely in 10 days. The patient returned to work on November 21.

CASE 4. H. B., a thirty-four-year-old woman, noted a "pimple" on the lip just below the right nostril on April 14, 1950. She believed it to be a "fever blister" and treated it with niter and antiseptics, but it became larger and itched and burned. On April 17, her face became swollen. She was seen by us on the 18th, when a large red oozing papule, 15 mm. in diameter, was found obstructing the right nostril; there was swelling of the corresponding side of the face and tenderness below the midjaw. Her temperature was 99.6°F. Results of antibiotic sensitivity tests are shown in Table 1. Because of the patient's "emotional" behavior and the presence of three infants in the household, she was hospitalized. Chloromycetin, 1 gm. every 6 hours, was ordered. The blood count showed a hemoglobin of 15 gm., a red-cell count of 4,970,000 and a white-cell count of 7100, with

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60 per cent neutrophils, 3 per cent eosinophils, 3 per cent monocytes and 34 per cent lymphocytes. The maximum sedimentation rate was 2 mm. in 1 hour (Cutler method). Urinalysis was negative. On the afternoon of hospital admission, the temperature had risen to 101.4°F., but it promptly fell to normal the next day. On April 19, the patient was less apprehensive. The right submaxillary lymph node and edema had disappeared, but the upper face showed increasing swelling, without redness. Clear serum oozed profusely from the lesion. Plasma titrations were done 2, 4 and 6 hours after a dose of 1 gm. of Chloromycetin; they showed 60, 45 and 30 microgm. per cc. respectively. On April 20, the swelling was a little more prominent over the right lower face. The left jaw was also slightly swollen, and a tender lymph node was palpable in the left submaxillary region. The orbital and paranasal zones were no longer edematous; the lesion was bluish-black and dry, and it had decreased somewhat in size. Smear and culture were repeated 42 hours after therapy had been instituted and 8 gm. was still palpable, but it was less tender. Smear and culture taken 48 hours after terramycin therapy was started and 4.5 gm. ingested revealed an occasional anthrax bacillus on the smear, but no growth was obtained. On May 4, there was only very slight local itching; the lesion was dry, flat and black, with a narrow ring of erythema around it, but there was no edema. The axillary node was smaller and no longer tender. Therapy was stopped after the ingestion of 6 gm. of terramycin in 3 days. The axillary node was no longer palpable when the eschar came off on May 11. The resulting shallow ulcer was completely healed in 12 days. The patient returned to work on May 15.

CASE 6. H. M., a forty-five-year-old man, was seen by us on May 12, 1950. On the 9th, he had noted a "pimple" just above the right ear; it was red, and itched. On the 10th, a large area of redness, swelling and tenderness developed in front of the ear. Because of the pain he consulted his family physician, who gave him an injection of 300,000 units of penicillin in oil, and sulfadiazine tablets by mouth. After three doses of the latter (1 gm. every 4 hours), the swelling spread under the right eye and the soreness increased. A second injection of 300,000 units of penicillin was administered on the 11th. On the next day he ingested 2 or more gm. of sulfadiazine (total intake, 9 gm.), and a third injection of penicillin (300,000 units) was given. The eye was less puffy, but the lesion oozed freely and there was marked pain in front of the ear and the angle of the right jaw. Anthrax was then suspected, and the patient was referred to us by his employer.

TABLE 1. *Bacterial Sensitivity Tests.*

CASE NO.	AUREOMYCIN microgm.	CHLOROMYCETIN microgm.	PENICILLIN microgm.	STREPTOMYCIN microgm.	NEOMYCIN microgm	POLYMIXIN microgm.	TERRAMYCIN microgm.
3	pi 0.1* ci 1.0	3.12	<0.1	3.12	5.0	>25.0	<0.1
4	pi 0.1 ci 1.0	3.12	pi 0.1 ci 1.0	pi 3.12 ci 12.5	5.0	>25.0	<0.1
5	pi 0.1 ci 1.0	3.12	<0.1	pi 3.12 ci 12.50	5.0	>25.0	<0.1
6	pi 0.1 ci 1.0	3.12	pi 0.1 ci 1.0	pi 3.12 ci 12.50	5.0	>25.0	<0.1
7	<0.1	12.50	pi 1.0 ci 5.0	pi 3.12 ci 12.50	pi 5.0 ci 25.0	>25.0	<0.1
8	<0.1	pi 3.12 ci 12.50	pi 1.0 ci 5.0	pi 3.12 ci 12.5	pi 5.0 ci 25.0	>25.0	<0.1

*pi = partial inhibition, ci = complete inhibition.

Examination revealed a typical anthrax papule; there was considerable tenderness, swelling and erythema of the upper face in front of the right ear; there was also swelling and tenderness at the angle of the right law. His temperature was 100°F. The results of sensitivity tests done on the culture obtained from the lesion are shown in Table 1. Examination of the blood revealed a red-cell count of 4,520,000, with a hemoglobin of 12.5 gm., and a white-cell count of 11,750, with 74 per cent neutrophils, 24 per cent lymphocytes and 2 per cent monocytes. The sedimentation rate was 51.0 mm. in 1 hour (Westergren method). Terramycin, 750 mg. every 6 hours, was ordered. Plasma titrations done ½, 1, 2 and 4 hours after ingestion of such a dose demonstrated the presence of 8 and 16 microgm. of terramycin per cc., respectively.

On May 13, the patient felt much improved. He had slept well, without the throbbing of face and neck which had kept him awake on the preceding three nights; the highest temperature (6 p.m.) was 100°F.; on this morning it was normal. There was no change in the lesion; a tender pealike preauricular lymph node was palpable; there was tight swelling over the mastoid bone as well as in front of the ear; loose swelling was noted under the chin, but no adenopathy was found. On May 15, there was no pain or soreness around the lesion, which was dry and black. The preauricular node was slightly tender and there was some edema over the right zygoma, but the face was almost normal in contour. Slight soft-tissue swelling was still noticeable under the chin.

A second smear and culture were taken after the ingestion of 9 gm. of terramycin in 3 days, and found to be nega-

of the drug had been ingested. The report was positive for anthrax. On April 21, the patient's condition was much improved. The face was less swollen; there was no adenopathy, local pain or tenderness. The lesion was dry and black; the eschar was lifted for a smear and culture, which were reported negative for anthrax. Chloromycetin was reduced to 750 mg. for two doses and then to 500 mg. every 6 hours. Plasma titrations, done 2, 4, and 6 hours after such a dose, revealed the presence of 20, 10 and 5 microgm. of Chloromycetin per cc., respectively. On the 23d, when she was discharged from the hospital, the lesion consisted of a tiny flat papule with an eschar 3 mm. in diameter Therapy was stopped after the ingestion of 16 gm. of the drug in 5 days. On April 24, the eschar came off; the sedimentation rate was normal. The patient returned to work on May 3.

CASE 5. V. K., a twenty-three-year-old woman, noted on April 28, 1950, a lesion on the right upper forearm that resembled a "blackhead," which was treated with Vick's salve. It had become larger and was itching on May 1, when she was seen by us. A typical anthrax pustule was found; the papule was surrounded by an area of erythema, 25 by 30 mm., with moderate edema. A large walnut-sized node and two smaller ones were palpable in the right axilla; they were quite tender. Her temperature was normal. The results of bacterial sensitivity tests are shown in Table 1. The red-cell count was 4,200,000, the hemoglobin 12 gm. and the white-cell count 11,800, with 68 per cent neutrophils, 30 per cent lymphocytes, 1 per cent basophils and 1 per cent eosinophils. The sedimentation rate was 21 mm. in 1 hour (Westergren method). Terramycin, 0.5 gm., every 6 hours, was ordered. Plasma titrations done at ½, 1, 2 and 4 hours after ingestion of such a dose revealed the presence of 8 and 16 microgm. of terramycin per cc., respectively. On May 2, the only complaint was that of itching around the lesion. There was some decrease in the local swelling, but the axillary adenopathy was unchanged. Smears taken 24 hours after therapy was started and 2 gm. of terramycin ingested showed the presence of a few anthrax bacilli. On May 3, the patient reported some nausea, but there was no vomiting. The edema was definitely decreased; the axillary node

tive for anthrax bacilli. Terramycin dosage was reduced to 0.5 gm., every 6 hours. On May 16, the swelling under the chin had disappeared and the face was normal in appearance; the preauricular node was still pea-like and tender. The lesion was black and dry. The white-cell count was 8850, with 54 per cent neutrophils, 43 per cent lymphocytes, 2 per cent eosinophils and 1 per cent basophils. The sedimentation rate was 33 mm. in 1 hour (Westergren method).

On May 18, terramycin therapy was discontinued after the ingestion of 15.25 gm. in 6 days. On May 20, the eschar began to separate at the periphery; it was removed on May 30. The ulcer healed completely in a week. The patient returned to work on May 29.

Case 7. N. S., a nineteen-year-old boy, developed a small papule "like a blackhead" on the right index finger on May 30, 1950. It itched a little, but there was no swelling until June 2, when the papule increased in size. The right axilla became painful on June 3, when the patient palpated a tender lump. On the 4th, he complained of malaise and headache; he felt "feverish." Clear serum oozed freely from the lesion. He was referred to us on June 5. A typical anthrax lesion was found, with swelling and erythema of the middle phalangeal joint of the right index finger. A tender walnut-sized node was palpated in the right axilla. His temperature was 100.2°F. Examination of the blood revealed a red-cell count of 4,640,000, with a hemoglobin of 13.5 gm. The white-cell count was 6750, with 61 per cent neutrophils and 39 per cent lymphocytes. The sedimentation rate (Westergren method) was 22 mm. in 1 hour. The results of sensitivity tests performed on the culture obtained from the lesion are shown in Table 1. Chloromycetin, 1 gm., every 6 hours, was ordered at 2:10 p.m. At 7:00 p.m. his temperature was 99°F. On the next day he felt better; there was less pain in the right axilla, and the joint was less swollen. On June 7, the axillary node was much smaller and the erythema around the lesion was less intense. From a grayish vesicle at the periphery of the papule, clear serum was obtained, which was shown to be positive for anthrax bacilli. On June 8, the dose of Chloromycetin was reduced to 500 mg., every 6 hours. Plasma titrations done at 1, 2, 3 and 4 hours after ingestion of such a dose showed the presence of 20, 10 and 20 microgm. of Chloromycetin per cc. A smear and culture of the lesion were now negative for anthrax (after ingestion of 11 gm. of Chloromycetin in 66 hours). On June 9, the axillary node was barely palpable; there was no swelling of the finger, and the lesion was dry, flat and black in color. Chloromycetin was reduced to 250 mg. every 6 hours. Therapy was stopped on the 10th after ingestion of 14.5 gm. of the drug in 5 days. The patient returned to work on June 12; the small eschar came off 3 days later, leaving a superficial ulcer that healed in a few days.

Case 8. P. M., a thirty-six-year-old man, noted on September 21, 1950, a small "pimple" in the left upper neck. It was associated with a local drawing sensation but with no constitutional disturbance. He was seen by us on September 22; a large papule 20 by 20 mm. was found below the left angle of the jaw. Its center was ulcerated and yellowish in color; considerable edema and induration surrounded the lesion, and two nontender lymph nodes were palpated in the lower posterior cervical chain. Chloromycetin, 750 mg. every 4 hours, was ordered.

On September 23, the patient had no complaints. The temperature was normal; the papule was moist and a little larger, and the upper third of the left side of the neck was more indurated and swollen. On September 24, the lesion had the typical appearance of an anthrax pustule. The vesicles and center of the papule had turned bluish-black in color, but the surrounding edema was not so great. On September 25, a smear from the lesion revealed an occasional anthrax bacillus. The neck showed lessened induration below and behind the left angle of the jaw. The white-cell count was 6000, with 66 per cent neutrophils, 31 per cent lymphocytes and 3 per cent eosinophils. The sedimentation rate was 3 mm. in 1 hour (Westergren method). On September 26, plasma titrations done at 1, 2, 3 and 4 hours after a 750-mg. dose of Chloromycetin revealed the presence of 20, 15, 7.5 and 15 microgm. per cc., respectively. The lesion was dry and flat; the edema of the neck was markedly reduced, and only one small postcervical lymph node was palpable. Smear and culture from the lesion were reported negative for anthrax bacilli. Chloromycetin was continued, 750 mg. every 6 hours. On September 27, there was slight swelling above the dry, flattened papule; a pea-like node was still palpable above the left clavicle. Chloromycetin was ordered, 500 mg. every 6 hours. On September 28, the eschar began to separate at its periphery, and the postcervical node was barely palpable. Chloromycetin dosage was reduced to 500 mg. every 8 hours. On September 29, therapy was stopped, after the ingestion of a total of 23.75 gm. in 6.5 days. The patient returned to work on September 30. On October 2, the eschar came off leaving a shallow ulcer that healed in 7 days.

Discussion

Our experience indicates that the newer antibiotics, aureomycin, Chloromycetin and terramycin, are efficacious therapeutic agents for the cutaneous manifestations of anthrax infection. Our observations confirm other recent reports.[2, 3] The favorable outcome of the cases treated correlates well with the demonstrated in-vitro sensitivities of the infecting strains of *B. anthracis* to the antibiotic agents employed.

Ingestion of aureomycin was accompanied in some patients by intense nausea and vomiting, whereas neither Chloromycetin nor terramycin was associated with any untoward reaction in this small group of patients. In our limited experience, all three agents seemed equally effective in controlling cutaneous anthrax. The dosage schedule employed in these cases was established arbitrarily; the matter of schedules deserves further investigation. However, it is evident that the dosage selected was effective and fulfilled the criteria of achieving circulating-plasma concentrations that exceeded many times the in-vitro sensitivity of the infecting organisms.

Local edema and erythema were controlled within 24 to 48 hours after therapy was instituted, but the regional adenopathy usually persisted for several more days. However, the pain and tenderness at the site of the glandular involvement subsided rather promptly. All signs of systemic reaction disappeared early in the course of treatment.

Anthrax bacilli were repeatedly recovered from lesions 2 and 3 days after the spread of local edema had been controlled, but the rate of their disappearance was not as prompt as that reported after larger doses of penicillin.[4-6] Our own experience with penicillin in cases of anthrax[7] has been at variance with previous reports, and paralleled the observations made in the group of patients under discussion. Moreover, we believe that the rates of disappearance of anthrax bacilli from pustules after the administration of various therapeutic agents cannot be too rigidly evaluated, since too many variable factors are involved.

The obvious advantage of oral medication, the nontoxicity and almost complete freedom from side-effects, and finally the economic advantages inherent in the ambulatory method of treatment, which does not require hospitalization, make the newer antibiotics, aureomycin, Chloromycetin and

terramycin, the preferred agents for the treatment of anthrax infection.

Conclusions

Eight cases of cutaneous anthrax were successfully treated with the newer antibiotics, aureomycin, Chloromycetin and terramycin.

The spread of local edema and erythema was promptly checked; regional adenopathy persisted for a few days, and smears and cultures from the lesions were negative for anthrax within 2 to 3 days after therapy was instituted.

Except for nausea and vomiting produced by aureomycin, no untoward reactions were encountered.

All patients but one were ambulatory and were treated at home.

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THYROID CRISIS ASSOCIATED WITH DIABETIC COMA*

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THAT the coexistence of two metabolic disturbances such as thyrotoxicosis and diabetes mellitus can cause an increased severity in both conditions has long been recognized.[1] These two conditions reach their most extreme states in the form of thyroid crisis and diabetic coma. The recent treatment of a case combining these two extremes has prompted the writing of this report.

Joslin and his co-workers have emphasized the high incidence of glycosuria and hyperglycemia in patients with hyperthyroidism.[2] In a large number of thyrotoxic patients they found that one third had fasting blood-sugar levels of over 130 mg. per 100 cc. Because of the disturbance in carbohydrate metabolism in the presence of hyperthyroidism, they have raised the usual critical fasting blood-sugar level to 150 mg. per 100 cc. for the diagnosis of diabetes mellitus. This resulted in an incidence of diabetes of 2.5 per cent in diffuse toxic goiter and of 4.3 per cent in toxic adenoma. Other series[3, 4] have indicated similar incidences. A true increase of diabetes over that found in the general population has been shown only in toxic adenoma and not in diffuse toxic goiter.[4] It also has been noted that improvement of coexistent diabetes on treatment of thyrotoxicosis by thiouracil occurred in toxic adenoma but not in diffuse toxic goiter.[5] This suggests a more direct relation between diabetes mellitus and toxic thyroid adenoma.

Clinical experience indicates that the onset of thyrotoxicosis may intensify the patient's diabetes. On the other hand, treatment of the thyrotoxicosis renders the diabetes less severe and more readily controllable.[6, 7] It has been conclusively shown that thyroidectomy for thyrotoxicosis usually makes the diabetes less severe. During the immediate postoperative period, however, a transient increase may occur in the insulin requirement of the patient.[6] On occasion this postoperative reaction has been exceedingly severe, and death has resulted.[8] It is possible that this phenomenon represents varying degrees of postoperative thyroid crisis. In contrast to the usual ultimate improvement of diabetes following thyroidectomy, a permanent increase in the insulin requirement has been reported.[9] This has not been satisfactorily explained.

The relation between diabetes and hyperthyroidism has led to the trial of thyroidectomy in euthyroid patients for the treatment of severe diabetes.[10] Rudy, Blumgart and Berlin[11] reported a case of uncontrollable diabetes with active pulmonary tuberculosis and normal thyroid function. Total ablation of the thyroid was performed, and the patient's insulin requirement fell postoperatively to half the preoperative dose, concurrently with depression of metabolic rate. When sufficient thyroid extract was given to elevate the metabolic rate to normal, the insulin requirement also returned to its previously high levels. The patient was then maintained on doses of thyroid extract sufficient only to prevent myxedema, and it was possible to keep the diabetes under control. A trial of anti-

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thyroid agents to produce hypothyroidism may be a useful adjunct in the treatment of severe diabetes with complicating tuberculosis.

Despite numerous experimental studies, the mechanisms of the effects of varying levels of thyroid activity on the pancreas and diabetes are not yet clearly understood. It has been shown[12] that thyroidectomy in rats affords protection against the diabetogenic action of alloxan or that of subtotal pancreatectomy. The effect of thiouracil is even greater, presumably because of the presence of sulfhydryl groups.[13] On the other hand, the administration of thyroid extract to rats previously treated with subdiabetogenic doses of alloxan resulted in diabetes.[14] In subtotally pancreatectomized rats, the administration of thyroid extract produces an initial increase in the incidence and severity of diabetes. However, with prolonged thyroid-extract treatment the diabetic state gradually disappears. In rats subjected to subtotal pancreatectomy but not treated with thyroid extract, diabetes eventually develops.[12, 15] In dogs with subtotal pancreatectomy, the diabetic state persists despite the prolonged administration of thyroid extract.[16] It is this species-difference that contributes to the difficulty of extending the interpretation of such experimental data to man.

Case Report

M. E. S., a forty-nine-year-old woman, was admitted to the Sixth Medical Service of the Boston City Hospital in a semicomatose condition.

The following history was subsequently obtained from the patient, her family and the family physician. Several months after the birth of her first child, 29 years ago, the patient first noted the presence of a swelling on the right side of her neck. This caused her no difficulty, and she sought no medical aid. The patient had been considered by her family to be irritable and "emotional" for several years preceding this admission. Six weeks before admission, she consulted her family physician because of "arthritis." He noted thyroid enlargement, a pulse rate of 120, a blood pressure of 200/80 and a basal metabolic rate of +69 per cent. He started a regimen of 300 mg. of propylthiouracil daily. Three weeks later the patient had gained 5 pounds and stated that she felt "wonderful." Eleven days before admission, after taking 100 mg. of propylthiouracil, she suddenly developed palpitation and therefore stopped taking the drug. On the following day, excessive thirst developed. Five days before admission she was again seen by her physician, who noted a 12-pound weight loss over a 2-week period, dehydration and a red urine reduction with Benedict's solution. Three days before admission she was afebrile, and her white-cell count was 10,000. The following day she vomited and was restless and dehydrated. That morning she took 100 mg. of propylthiouracil for the first time after a lapse of 9 days. She was seen by her physician, who gave her 15 units of regular insulin and left instructions for her urine to be tested. Because of her continued restlessness, the family called another physician, who administered an injection of morphine. The patient became quiet for several hours, but during the next 36 hours she was alternately agitated and stuporous, with vomiting, polydypsia and polyuria. She was therefore brought to the hospital by ambulance.

The only other significant datum that could be elicited was the presence of diabetes in the patient's mother and possibly in several of the patient's siblings.

On admission, physical examination revealed a well developed middle-aged woman, semi-comatose, with Kussmaul breathing. Her rectal temperature was 97°F.; her pulse was 132. Respirations were 32, and the blood pressure was 105/40. Her skin was cool and dry. The head revealed no evidence of trauma. Her eyes were prominent, without marked decrease in the intraocular tension. There was no aural discharge or inflammation. The tongue and mucous membranes of the mouth were dry. Her neck was supple. In the right upper pole of the thyroid gland there was a smooth, soft nodule measuring 5 cm. in diameter. The remaining portion of the gland was not enlarged, and no bruit was audible. Her lungs were clear to percussion and auscultation. The heart was not enlarged to percussion. The rhythm was regular, with occasional extrasystoles. No murmurs were heard. The liver edge was palpable 2 finger-breadths below the right costal margin. Pelvic and rectal examinations done subsequently were normal. Deep-tendon reflexes were ++ throughout, and no pathologic reflexes were elicited.

Initial laboratory examinations revealed a hemoglobin of 13 gm. and a hematocrit of 40 per cent. The corrected sedimentation rate was 35 mm. per hour (Wintrobe method). The white-cell count was 9000, with a normal differential. The blood sugar was 500 mg., the carbon dioxide combining power was 13 vol. and the nonprotein nitrogen was 91 mg. per 100 cc. Examination of the urine revealed a red reduction for sugar and a ++++ acetone test, with a negative sediment.

Therapy with insulin and parenterally administered fluids was started on admission. During the first 6 hours, she received a total of 350 units of regular insulin, intravenously and subcutaneously, and 6000 cc. of fluids intravenously (an isotonic saline solution followed by a 5-per-cent solution of dextrose in water). As a result, her glycosuria was under control and her urine free of acetone by the end of this interval. Although the urine remained free of acetone thereafter, the blood carbon-dioxide values were slow to return to normal. About 6 hours after admission, although the patient was able to take fluids orally, she became increasingly restless, her temperature rose, her cardiac rhythm was markedly irregular, and her respirations, no longer Kussmaul in nature, were rapid, shallow and irregular. Her tendon reflexes were less active than on admission. An electrocardiogram showed sinoauricular tachycardia, with many ventricular premature beats and no prolongation of the QT interval. Because of these findings, additional therapy of two kinds was started. During the next 12 hours she received by mouth two liters of orange juice to which 14 gm. of potassium chloride had been added. Eight hours after admission, and again 16 hours after admission, she received 1 gm. of sodium iodide intravenously. Parenteral injection of fluids containing saline, dextrose, insulin and vitamins was continued throughout the day. During the first 24 hours her total fluid intake was almost 19 liters, with a urinary output of 7 liters. Despite almost continuous alcohol sponge baths, her rectal temperature rose to 103.6°F. Because of continued restlessness, she received several injections of sodium luminal during the evening. Prophylactic penicillin, oxygen given by nasal catheter, and constant urinary drainage were started.

At the beginning of the second hospital day, the patient was still febrile (rectal temperature, 105°F.), restless, tachypneic (respirations, 40). Her skin was hot and flushed. She had tachycardia, with occasional premature beats. Her deep-tendon reflexes could not be elicited in the lower extremities and were 1+ in the upper extremities. The lungs were clear to auscultation, and a chest x-ray film showed only mild congestive changes. An electrocardiogram showed a decrease in ventricular irritability. Studies of the blood, made during a glucose infusion, showed a blood-sugar level of 350 mg., a blood urea nitrogen of 16 mg. and a carbon-dioxide combining power of 35 vol. per 100 cc., with a serum sodium of 145 milliequiv. and a serum potassium of 1.9 milliequiv. per liter. The patient was given a third intravenous injection of 1 gm. of sodium iodide; this was repeated at 12-hour intervals until the end of her 4th hospital day. Glucose, parenterally administered, was continued, and a slow intravenous infusion containing 8 gm. of potassium chloride in dilute solution was started. High-caloric feedings and 0.2 gm. of quinidine, 4 times a day, were administered by gastric tube. Alcohol sponge baths, insulin, and nasal oxygen were continued. Toward the end of the 2nd hospital day, her temperature fell to 100°F., her respirations were less rapid and she responded when addressed by her name.

On the morning of the 3rd day, the patient appeared improved; she recognized members of her family. She con-

tinued to toss about restlessly; her temperature was 101.2°F., and her pulse rate was 128. The remainder of the examination was no different from that of the previous day. Laboratory findings revealed a blood sugar of 444 mg., a. carbon dioxide combining power of 52 vol. per 100 cc., a blood urea nitrogen of 22 mg., a plasma chloride of 122, a serum sodium of 150 (blood drawn during saline infusion) and a serum potassium of 5.3 milliequiv. per liter. Complete urinalysis showed no abnormalities other than glycosuria. She continued on the same therapeutic regimen. Later in the day she was able to respond rationally to questioning and was fully oriented.

Examination on the 4th day revealed that the thyroid nodule was 1.5 cm. less in diameter than on admission and was quite firm. The patient was able to converse. She asked for and took soft solids by mouth. During this day propylthiouracil was started, in doses of 200 mg., 3 times a day. Toward evening, her temperature rose to 102.8°F. Urinalysis revealed a sediment loaded with white blood cells.

On the 5th day, the patient was able to eat regular meals. Stomach tube, nasal oxygen and parenterally administered fluids were discontinued, and Lugol's solution (15 drops 30 times daily) replaced the intravenous injection of iodine. Prophylthiouracil was continued. Her metabolic rate was +69 per cent. The indwelling bladder catheter, which had been inserted on admission, was removed. On the evening of this day, her rectal temperature fell to 99.6°F.

On the 6th day, the patient remained afebrile. Her pulse rate ranged between 90 and 110. The urine sediment was clear. Another metabolism test yielded a value of +73 per cent. The blood cholesterol was 102 mg. per 100 cc. The bromsulfalein test revealed only a trace of dye retained at the end of 45 minutes. The cephalin-cholesterol flocculation test was negative. At no time during the hospital course was an elevated icteric index noted.

Examination on the morning of the 7th hospital day revealed a well developed, well nourished woman, in no distress. Her eyes were prominent, and a marked lid-lag was present. The thyroid gland was diffusely enlarged to about three times normal size with the right upper pole more prominent and with several small irregularities palpable elsewhere. The gland was firm. No bruit was heard. From the 6th hospital day on, the patient had expressed an increasing desire to leave the hospital. On the 8th hospital day, after refusing to take insulin or propylthiouracil, she signed out of the hospital against advice. Both the patient and her family were apprised of the necessity of continued medical supervision.

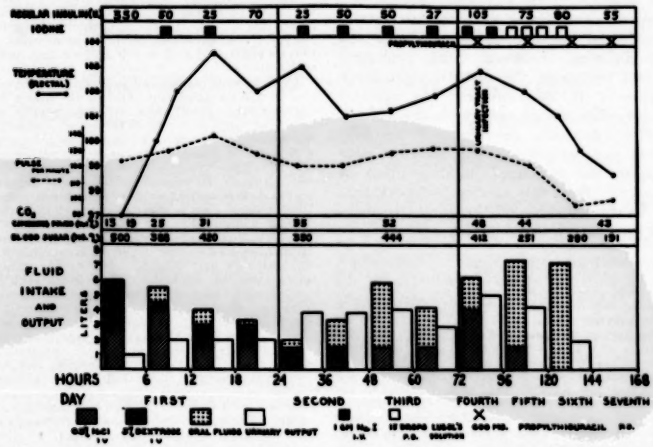

FIGURE 1.

DISCUSSION

Diabetic coma has a well defined clinical and laboratory picture, and the diagnosis generally can be made promptly and without difficulty. Thyroid crisis, however, is rare, and conformance to clear-cut criteria frequently does not occur. The management of the latter condition represented the principal problem in this case. Here, as in two similar cases reported in the literature,[17] the diabetic state found on admission responded rapidly to treatment.

Thyroid crisis is not a specific entity, but rather the sum total of the effects on the many body systems of fulminating thyrotoxicosis. McArthur and others[18] have defined thyroid crisis as "a life-endangering augmentation of the symptoms of thyrotoxicosis in which the patient's response is out of proportion to the exciting stimulus, whatever its nature." Thyroidectomy, severe infection, diabetic acidosis and cardiac decompensation have been noted to precipitate thyroid crisis.[19] Minor surgical procedures, such as tonsillectomy, tooth extraction and abdominal paracentesis, have been implicated as precipitating causes.[20] In the past three

decades, thyroid crisis has caused the death of about 1 per cent of all thyrotoxic patients seen.[18, 21, 22] During this period, it was responsible for approximately half of all deaths due to thyroid disease, including those resulting from surgery and neoplasm of the thyroid.[23, 24] The mortality rate of thyroid crisis itself in some series is as high as 66 per cent.[18, 21, 22] Death in "medical" crisis was more frequent than in postoperative crisis.[18, 23, 24] However, with the advent of effective antithyroid agents and the improvement of surgical technic, the incidence of thyroid crisis has greatly diminished. The clinical picture of thyroid crisis is the result of rapidly progressing fulminating thyrotoxicosis. The most striking features are those referable to the central nervous system: delirium, irritability and coma. Profound weakness, tachycardia and cardiac arrhythmias are seen. Fever frequently dominates the picture; the temperature may range from 100° to 106°F. It should be emphasized, however, that hyperpyrexia is not a *sine qua non* for the diagnosis of thyroid crisis. The presence of diabetic acidosis, as this case illustrates, may result in only a slightly elevated or even subnormal temperature. As the ketosis is brought under control, the temperature begins to rise (Fig. 1). Root,[17] in his report of two cases of combined thyroid crisis and diabetic coma, also noted an initially low temperature during the period of diabetic acidosis. Also, in "apathetic hyperthyroidism," as described by Lahey,[25] the usual clinical picture is not present. When apathetic crisis occurs, there is prostration, muscle atrophy, apathy and a temperature usually not above 101°F.[26]

A study of blood electrolyte levels during thyroid crisis has shown no characteristic abnormalities.[27] However, careful attention must be paid to water and electrolyte balance during the treatment of these cases. This attention is even more strongly indicated when thyroid crisis is complicated by diabetic coma. During the stage of acidosis, the fluid and salt deficit must be replaced. With a high temperature and hypermetabolism, extraurinary loss of water may be great. During the first twenty-four hours of her course, this patient was given 19 liters of fluid, while her urinary output was only 7 liters. Constant surveillance revealed no evidence of peripheral or pulmonary edema. She apparently lost a large quantity of water through the skin and lungs. This patient developed a significant degree of hypokalemia, which followed the administration of large amounts of insulin and glucose and a large urinary output.[28] The presence of a low serum potassium should be corrected by the oral or parenteral administration of potassium salts. Large amounts of potassium were necessary to restore to normal this patient's serum level. The electrocardiographic changes usually ascribed to hypokalemia[29] were not found here.

It has been emphasized that there are no pathognomonic clinical or pathologic features common to all cases of thyroid crisis.[18, 19] Postmortem findings indicate a breakdown in one or more body systems. The occurrence of liver damage in thyrotoxicosis is well known.[30] Hepatic necrosis is a common finding at death in thyroid crisis.[31] Maddock[27] found abnormal liver function tests but no correlation between the severity of the thyroid crisis and the degree of impairment of function. The few tests performed in our case showed no evidence of hepatic dysfunction.

Treatment of thyroid crisis has two aspects. One is directed against the many facets of hypermetabolism and its consequences, and therefore consists of the following: sponge baths and even ice-water enemas to combat pyrexia; parenterally administered fluids containing glucose and suitable electrolytes to correct dehydration, hepatic glycogen depletion and electrolyte disturbances; oxygen to prevent tissue anoxia and sedation for the irritability. Prophylactic chemotherapy and vitamins should be given. It has been suggested that adrenal cortical extract may be of value to compensate for possible adrenal cortical exhaustion.[18] Improvement after spinal anesthesia has been reported.[32] The second aspect of treatment is aimed at diminishing thyroid activity. In the past, iodine has been used as standard therapy. Since their introduction, the use of the newer antithyroid agents, such as propylthiouracil, has been suggested as adjuvant therapy.[18, 22] However, the administration of iodine reduces the output of thyroid hormone[33] and affords as rapid a means as is available to control thyrotoxicosis.[34] In the acute emergency of thyroid crisis, therefore, the intravenous injection of iodine is indicated because of its speed of action. Propylthiouracil may be used later to continue the antithyroid effect of the iodine. If one desires to use radioactive iodine because of its long-term effect it should be administered prior to regular iodine therapy. This is to ensure an adequate uptake of radioactive iodine by the thyroid gland.

Summary

Clinical experience indicates a close relation between thyrotoxicosis and diabetes mellitus. Despite considerable experimental data, the mechanisms involved are not clearly perceived. The simultaneous occurrence of thyroid crisis and diabetic coma is a rarity, and the presence of the latter may obscure the clinical picture of the thyroid crisis. A case of this combination is presented, and the metabolic disturbances noted are discussed. The treatment of thyroid crisis consists of iodine, as an antithyroid agent, and suitable measures to combat the multiple effects of hypermetabolism.

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PHARYNGEAL AND LARYNGEAL SYMPTOMS OF THYROID ORIGIN*

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IT IS the purpose of this paper to point out some of the pharyngeal and laryngeal symptoms of thyroid origin and the lesions they may represent.

Sore Throat

The fact that sore throat can be a symptom of thyroid disease is not new, but it is not generally realized by practicing physicians. Crile and Rumsey[1] have demonstrated in a recent study the chief complaints in a series of 38 cases of subacute thyroiditis. These are listed in the table below:

Chief Complaint	No. of Cases
Sore throat	9
Sore neck	6
Swelling in neck	4
Pain and swelling in neck	3
Lump in throat	3
Sore lump in neck	2
Nervousness	2
Thyroiditis	1
Pain in thyroid	1
Goiter	1
Pain in ear	1
Pain in jaw	1
Pressure in throat	1
Weakness and fatigue	1
Hot flushes	1
Menopause	1

*From the Student Health Service, University of California. Presented at the annual meeting of the Southern California Chapter of the American College of Surgeons, April 14, 1950, Los Angeles.

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As seen in the table, sore throat was the commonest chief complaint of all, and it was shown by the authors that the administration of x-ray therapy (800 r) to the thyroid gland produced a disappearance of symptoms within seventy-two hours.

CASES 1 AND 2. In recent months, two male patients have been seen by me who had characteristic sore throats, in both instances of three weeks' duration. They felt pain on swallowing, with the sensation of a "lump" in the lower neck; the pain radiated to the ears. These complaints resembled those of a post-tonsillectomy patient. One patient, 26 years old, had been treated previously with large doses of penicillin with no relief; the other, aged 31, had been given ear drops and had been referred to an exodontist for the extraction of a third molar.

The pharynx, hypopharynx, and larynx were carefully examined to rule out the possibility of pharyngitis, tonsillitis or lingual tonsillitis; no redness or exudate was found in the throat. Palpation of the thyroid gland, however, revealed marked tenderness and, in one case, a diffuse enlargement. The sedimentation rate was decidedly elevated in both patients. The diagnosis of subacute thyroiditis was therefore considered appropriate. X-ray treatments were administered, and relief was prompt.

Lump Sensation in Throat

Many patients who complain of the sensation of a lump have a thyroid disturbance of some nature, yet are tagged with the diagnosis of globus hystericus or psychoneurosis and are treated by suggestion and sedation. Most commonly this symptom is due to hypothyroidism and is relieved by the administration of thyroid. In these cases there is usually no enlargement of the tissues of Waldeyer's

ring, whereas in hyperfunction there is often a hypertrophy of these lymphoid structures.

In addition, it has been shown that thyroiditis may be present with no attendant pain. Here again, a lump sensation may be a prominent complaint. If the sedimentation rate is elevated, this possibility must be considered. Two other causes of a lump sensation referable to the thyroid gland should be mentioned: lingual goiter, which is rare, and the not uncommon thyroglossal cyst.

Case 3. A 54-year-old woman complained of a lump sensation in her throat of two years' duration. She was worried about the possibility of cancer, but had been told by another laryngologist that the condition was due to "nerves." She was not relieved by sedation. Examination of the ear, nose and throat was negative.

The blood cholesterol was 290 mg. per 100 cc. The patient was relieved by taking 65 mg. of thyroid daily. Her symptoms recurred when dosage was changed, without her knowledge, to a vitamin preparation taken by mouth in place of the thyroid extract.

Preoperative Hoarseness

This may occur with marked thyroid deficiency, which results in a thickening of the cords, or it may occur as a result of laryngeal paralysis. It is therefore essential to good surgical management that laryngoscopy be performed before and after thyroid operations.

Case 4. A recent example of a unilateral preoperative paralysis due to pressure on the nerve from an adenoma was seen by me in a fifty-three-year-old woman. She insisted that she had experienced only transient hoarseness and one or two episodes of aphonia. At the time of operation, it was seen that the neoplasm was located sufficiently posteriorly to stretch the right inferior laryngeal nerve taut. The palsy disappeared four months after subtotal thyroidectomy.

Postoperative Hoarseness

When due to unilateral paralysis, postoperative hoarseness may result from scarring or edema as well as from the cutting of the inferior or recurrent laryngeal nerve. It produces a weak, rough voice, difficulty in swallowing liquids due to their spilling over into the partly closed glottis and an irritative cough due to aspiration. The voice changes last as long as the paralysis, and the patient is unable to raise his voice to shout or sing. However, the dysphagia is soon overcome, and swallowing is usually not bothersome after three weeks. No satisfactory treatment is known. The procedures employed for bilateral paralysis are not applicable in the case of unilateral palsy.

When due to bilateral paralysis, postoperative hoarseness is a tragic condition, having several dangerous aspects. First, the cords cannot be abducted; they remain close together, appreciably shutting off the airway. This may demand an immediate tracheotomy or it may simply limit the amount of physical activity possible, because of dyspnea. Secondly, the dyspnea may not manifest itself until six to eight hours after the operation, when the cords assume the nearly midline position. The surgeon may be completely unaware of the trouble until it is too late. Thirdly, the repair of this injury is not uniformly successful. If the function is to return, it will usually do so within four months.

Needless to say, the best therapy for bilateral palsy is prophylaxis against such surgical accidents or errors. Some paralysis is only temporary, resulting from edema, and will clear spontaneously in two to four months. As for treatment after tracheotomy, many surgical procedures have been proposed following King's[2] suggestion. In my experience, the technic of Woodman[3] has proved technically easier, and the results are equal to, and sometimes better than, any other method. Recently, I have added a step to the procedure. After the arytenoid cartilage has been removed the Roberts suspension laryngoscope is inserted, and the effect of the suturing and retraction of the true cord is thus easily watched throughout the final stages.

When this technic of arytenoidectomy was used, it was successful in producing an adequate airway and a satisfactory voice in the majority of cases. One failure was caused by a hematoma in the area of the arytenoid defect that persisted and narrowed the glottic chink. Another patient insisted on using a tracheotomy tube, in spite of having an adequate airway, because of an anxiety neurosis.

Case 5. A thirty-four-year-old woman underwent a thyroidectomy for cystic adenomas of both lobes of the gland. Hoarseness and extreme dyspnea were noted on the evening after the operation. She states that she was "saved by using oxygen." No examination was made of the larynx, and no tracheotomy was performed.

Because her complaints persisted for two years she consulted me; a bilateral abductor paralysis was seen. A modified Woodman arytenoidectomy was performed, and the dyspnea vanished. The voice was stronger after the operation, but not normal.

Case 6. A sixteen-year-old girl underwent a total thyroidectomy for carcinoma of the thyroid gland. Hoarseness was apparent immediately after she regained consciousness, but there was little dyspnea. There had been no intubation for endotracheal anesthesia. Examination demonstrated a bilateral abductor paralysis with about a 3-mm. space between the true cords. No therapy was advised at that time.

She was seen four months later; she now spoke clearly, with a normally functioning larynx as shown by mirror examination. X-ray therapy had been given postoperatively and radioactive iodine had been administered without demonstration of residual thyroid tissue. There was no evidence of recurrence.

Summary

Thyroid disease may manifest itself by various pharyngeal and laryngeal symptoms alone. The laryngologist, therefore, should be constantly aware of the relation of such symptoms to this condition.

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FIFTY YEARS OF MEDICAL PROGRESS

MEDICINE AS A SCIENCE: NEUROLOGY

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AS IS the case with the other special disciplines of medicine, neurology has been profoundly affected by changes in medicine during the last fifty years, from both within and without its own special field.

The sulfonamides and antibiotics almost wiped out the infections, and even the two major enemies of 1901, tuberculosis and syphilis, were greatly weakened. Little headway was made against poliomyelitis, multiple sclerosis and the intrinsic degenerative processes, but their attendant problems were better defined and plans for combating them were better organized and co-ordinated.

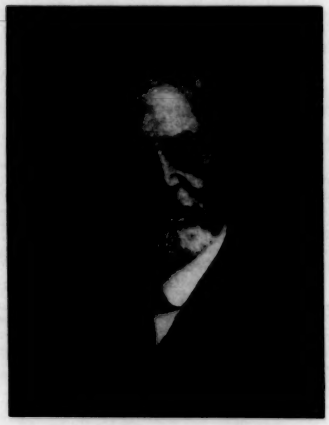

FIGURE 1. *James Jackson Putnam (1846–1918), Apprentice "Electrician" to the Massachusetts General Hospital, June 25, 1872.*

Pharmacology, physiology and anatomy have brought about many changes in the daily tasks of the neurologist of 1951. To understand this change, let us visualize neurology in 1901, using as a convenient example a day in the life of James J. Putnam of Boston. Putnam was typical of the best men of his time, a conscientious, farseeing, scholarly man, modest and hard-working. A graduate of Harvard College and the Medical School, intern at the Massachusetts General Hospital and visitor to Leipzig, Vienna and London, he returned to Boston in 1872 to establish one of the first neurologic clinics in the United States.

By 1901, with growing out-patient responsibilities at the Massachusetts General Hospital, he occupied there a small room to which were brought each morning all the hospital cases that were not understood, a rare lot from the medical and surgical wards. Few internists were interested in neurology in those days; most of them were woefully ignorant of the form and function of the nervous system. The surgeons were even less knowledgeable, but Putnam in his little room under the entrance arch, justly called the "cloaca maxima," was their one hope; much to their surprise, he was often helpful — and always earnest and gracious.

There sat a most unusual man, friend to all the staff, equipped only with an ophthalmoscope and a percussion hammer for diagnosis and an electric battery and bromide for treatment. Not quite! Putnam's first-class brain and his cautious deductions and deep understanding of what we now call psychosomatic medicine were also present. Well trained in pathology, with a neuropathological laboratory in his own house, there being no provision for such in the hospital, Putnam spent the mornings at the hospital and the afternoons in his consulting-room at home; evenings he devoted to reading the works of Gowers, Jackson and his other contemporaries, with whom he frequently corresponded.

In the practice of neurology, syphilis was an important subject; iodide of potassium and mercury were the bulwarks of defense. For epilepsy, bromides were used; for exhaustion, strychnia; for pale people, iron or arsenic; for neuritis, salicylates and antipyrine. Electricity — galvanism or faradism — was used for neuralgia, paralysis, ataxia — even for chorea and hysteria. For the last, valerian and asafetida were "often of service" (Osler). Although he perhaps had done no lumbar punctures by 1901, Putnam was familiar with the clinical signs of spotted fever, knew confluent smallpox and the nervous manifestations of typhoid fever, recognized quickly the "policeman's tip" and might well have seen *Bacillus welchii* and some of the early x-ray pictures that were ground out so painfully and dangerously by Walter Dodd, the apothe-

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cary and photographer to the hospital, and his assistant, Joseph Godsoe.

Literature of 1901

The chief neurologic textbook used in 1901 — and one of the best of all time — was Hermann Oppenheim's "Lehrbuch der Nervenkrankheiten" (1894). The English translation did not appear until after the fifth German edition in 1911. Oppenheim's book exerted the greatest influence on neurology of any text ever published, save perhaps Gowers' "Manual of Diseases of the Nervous System," issued in two volumes in 1886 and 1888. Of the other books, mention may be made of Romberg's "Lehrbuch der Nervenkrankheiten des Menschen" (1846), frequently reissued; S. W. Mitchell's "Injuries of Nerves and Their Consequences" (1872); Charcot's "Leçons sur les maladies du système nerveux faites à la Salpêtrière," in five volumes (1872–1893); Erb's "Handbuch der Krankheiten des Nervensystems," in two volumes (1876–1878); Bastian's "Paralyses, Cerebral, Bulbar, and Spinal" (1886) and Remak and Flatau's "Neuritis und Polyneuritis" (1899).

In 1899 Gowers, with the aid of James Taylor, revised and enlarged his "Manual," and it was published in two volumes as a third edition. In this work of the most acute and accurate observer of his time is found a reflection of neurology as it was known at the turn of the century. It was, however, an age of freedom from bibliography, and where the professor found his authoritative information was rarely disclosed. Gowers did not fail to note such important additions to neurologic literature as R. W. Smith's "Treatise on Neuroma," an outstanding book of 1849, Henry Head's early work (1893) on the segmented distribution of sensory nerves following herpes zoster, the description by Ferrier and others of the gradual revelation of the spinal roots involved in Erb's palsy, Ross and Bury's "On Peripheral Neuritis," the concepts of acute infections — myelitis due to syphilis, gonorrhea, typhus and typhoid fever, and the importance of Todd's observations, made in 1847, on tabes dorsalis. Gowers was conservative in his attitude toward the much debated question of "primary" spastic paraplegia, or lateral sclerosis, but saw no reason that it should not occur. He gave credit to Putnam for his description of combined system disease in 1891.

The fourth edition of Osler's "Textbook" was revised in the first few months of 1901 and published in the same year. Cushing records that Osler was "knee-deep" in proofs by the end of May. Campbell and Bramwell's analysis of myasthenia gravis (*Brain*, 1901) was not overlooked. Osler found Putnam's description of ataxic paraplegia, now known as combined system disease, interesting because of "the relation of this group to anemia." He relied heavily on the neuropathological acumen of E. W. Taylor, then a young man in Boston, fresh from Oppenheim's laboratory in Berlin.

Osler classified general paresis as a chronic diffuse meningoencephalitis, an important predisposing cause being, as noted by Mickle, "a life absorbed in ambitious projects with all its strongest mental efforts, its long-sustained anxieties, deferred hopes, and straining expectation." The important individual factor was recognized as syphilis, but Fournier's ideas were not fully accepted, although carefully weighed.

In a few instances tumors of the spinal cord were thought to be amenable to surgical treatment, Osler no doubt having in mind Horsley's famous case, studied with Gowers in 1888. Brain tumors were limited, except for the metastatic types, to glioma and neuroglioma. At least four fifths of all cases were considered unsuitable for operation, although a few tumors had been successfully removed by Macewen, Horsley, Keen and others. Acute encephalitis was almost unknown, but Osler mentioned J. J. Putnam's description of a case following mumps. Acute febrile polyneuritis was then recognized, and recurring multiple neuritis had recently been reviewed by Henry M. Thomas. Anesthesia paralysis had been recorded by Garrigues in 1897. All the cranial nerve palsies were known by 1900, and Osler gave a full account of them. He added much to our knowledge of chorea.

Bromides were the only form of treatment for epilepsy other than the Jacksonian type; in that, Osler thought, "The propriety of surgical interference is universally granted." The specific surgical treatment of trifacial neuralgia had not been thought of. Hysteria was recognized as a mental and emotional anomaly; Osler wrote: "The important element in the treatment is moral control." The relation of the pituitary glands to acromegaly was known, but only one attempt to extirpate the pituitary body had been made, by Richard Caton of Liverpool in 1893 — and that was unsuccessful. Alfred Fröhlich's description of dystrophia adiposogenitalis came out too late in 1901 to be included.

Putnam also had recourse to periodical literature. The *Deutsche Zeitschrift für Nervenheilkunde* and the *Archiv für Psychiatrie und Nervenkrankheiten* were undoubtedly old friends, as were the *Revue neurologique*, *Brain*, *The Journal of Nervous and Mental Diseases* and a few others. Putnam was an active member of the American Neurological Association (1875) and contributed frequently to its *Transactions*, as well as to the *Journal*.

1901–1910

At the close of the previous century, Head and Campbell published their studies on herpes zoster, demonstrating the pathologic changes in the posterior nerve roots and delineating the sensory skin fields, the first of a long series of papers by Henry

Head that culminated in a two-volume work, "Studies in Neurology," issued twenty years later. The site of the lesion had been noted by Bärensprung as early as 1861. In the same year Hermann Oppenheim described amyotonia congenita, separating this disease from myotonia congenita, or "Thomsen's disease," and Risien Russell and his co-workers, Batten and Collier, gave the first full description of subacute combined degeneration of the spinal cord, thus augmenting Putnam's work of 1891. Mills, who had coined the term "neuronitis" two years before, called attention to the unilateral type of progressive ascending paralysis, a diagnosis not readily accepted in later years as descriptive of a specific disease. Harvey Cushing outlined a new method of total extirpation of the Gasserian ganglion for relief of pain in cases of trigeminal neuralgia by cutting through the temporal fossa beneath the middle meningeal artery. The paper was accompanied by a plate showing the base of the skull, skillfully drawn by Cushing. The year closed with the publication of Hans Laehr's great three-volume history, "Die Literatur der Psychiatrie, Neurologie und Psychologie von 1459–1799" (1900), a publication of outstanding merit.

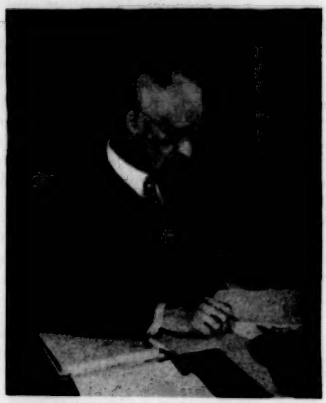

FIGURE 2. *Harvey Cushing (1869–1939). (Courtesy of Dr. Richard U. Light. Reproduced from Baumgartner, L.: Harvey Cushing as book collector and littérateur.* Bull. Hist. Med. *8:1055-1066, 1940, with the permission of the publisher.)*

In 1901 Gerrit Grijns, who had succeeded Eijkman as director of the Research Laboratory in Batavia, pronounced beri-beri a "deficiency disease," following Eijkman's experimental production of the disease in fowl. This opened a new chapter in our understanding of some forms of polyneuritis. Of equal importance was the stimulation given in the same year by Alfred Fröhlich of Vienna, who described the syndrome of dystrophia adiposogenitalis with pituitary tumor, obesity and sexual infantilism. In neurosurgery Spiller, a neurologist, and Frazier, a surgeon, improved the surgical treatment of trigeminal neuralgia by advocating division of the sensory root in place of the more dangerous method of removing the Gasserian ganglion, described by Cushing the year before.

Max Nonne published in 1902 his exhaustive treatise on "Syphilis und Nervensystem," the first full consideration of neurosyphilis as a whole. In the same year, Déjérine and Thomas considered the diseases of the spinal cord in their scholarly summary of that subject. From the clinic, Gowers discussed myopathy and described the distal form of progressive muscular dystrophy.

Oskar Vogt published his studies on the cerebral cortex in 1903, furthering the work initiated by Betz, Lewis and Retzius. Froin initiated the study of the cerebrospinal fluid with his investigations of the inflammatory reactions of the meninges, calling particular attention to the protein content. Of perhaps more immediate importance was a report on the successful transmission of syphilis from man to the higher apes by Metchnikoff and Roux, working in the Pasteur Institute in Paris. Their investigations gave new impetus to the study of syphilis by such workers as Fournier, Jarisch and Herxheimer. The discovery of the causal organism was accomplished by Schaudinn and Hoffmann in 1905. In the meantime, Fischer and Mering (1904) synthesized veronal (barbital), a drug that, with its derivatives, was to have great influence on the treatment of neurologic disease.

By 1905 Henry Head, working with Sherren, was ready to report on the newer aspects of the whole afferent nervous system and the consequences of injury to peripheral nerves in man. In the same year A. W. Campbell augmented Vogt's investigations of the cerebral cortex with histologic studies of localization of cerebral function. Harvey Cushing continued to explore the field of brain surgery, revealing new aspects of the subject by describing an operation for intracranial hemorrhage of the newborn and advocating subtemporal decompression in the treatment of inaccessible brain tumors.

Head, with Thompson, continued his investigations on the afferent system, following his previous work on the peripheral nerves, by grouping the impulses within the spinal cord. In 1906 Déjérine, with Roussy, published his description of the "thalamic syndrome." At the same time Marie attempted to bring some order to the complicated problem of aphasia by his classification of anarthria, Broca's motor type and Wernicke's sensory aphasia. Cushing continued his studies on the hypophysis and described sexual infantilism and optic atrophy in a patient with a pituitary tumor, thus again calling

attention to the remote glandular effects of pituitary disorders as well as the direct pressure causing blindness. Hermann Schloffer developed the nasal approach to pituitary tumors in an operation described in 1906 and further elaborated in 1907. Wassermann, Neisser and Bruck announced their serodiagnostic reaction for syphilis, later known as the "Wassermann test"; its value in the examination of the cerebrospinal fluid was demonstrated by Wassermann and Plaut in the same year, thus serving to establish syphilis as the cause of both tabes dorsalis and general paresis. The long controversy set off by Fournier in 1894 was thus drawn to a close. The most outstanding contribution of 1906, however, was the publication of Sherrington's "Integrative Action of the Nervous System," which had a profound influence on neurologic thought and clinical physiology.

In 1907 Simon Flexner announced his antiserum for the treatment of cerebrospinal meningitis; Gowers defined the borderland of epilepsy; Jean Cruchet published an important monograph on spasmodic torticollis; G. Elliot Smith issued a new topographical survey of the human cerebral cortex, outlining distinct cortical areas, thus advancing the work of Vogt and Campbell. Pirquet von Cesenatico introduced the word "allergy" into medicine in relation to vaccination.

In the following year, Flexner and Jobling reported on the clinical use of serum in the treatment of meningitis in man — a landmark in the development of our knowledge of specific therapy. Rivers and Head described an experiment in nerve division, Head having submitted to a division of his left radial and external cutaneous nerves. He subsequently observed the course of regeneration and as a result was able to reclassify the sensory pathways. Also in 1908, Marcus Schwalbe defined dystonia musculorum deformans, or "torsion-spasm," and Dixon and Hamill noted the similarity of the effects of nerve action and of certain drugs — notably muscarine — on the heart.

Korbinian Brodmann published his study of cytoarchitectonics in 1909, outlining a numbered plan of the various areas of the cortex that is still in use. In neurosurgery, Foerster and Küttner advocated section of posterior roots in the treatment of gastric crises in patients with tabes dorsalis, a striking innovation that set off a long series of surgical attacks on the peripheral and autonomic systems in an attempt to alleviate intractable pain and other symptoms. Finally, Landsteiner and Popper announced the transmission of poliomyelitis to monkeys, thus opening the way to the viral and clinical studies of a later era.

The functions of the pituitary body were briefly outlined by Cushing in 1910, and Cushing, with Crowe and Homans, introduced the first experimental evidence of the relation between the pituitary and the reproductive systems in their report on experimental hypophysectomy. At the same time, Dale and Laidlaw noted the physiologic action of histamine and Reid Hunt and Taveau described the toxicity and chemical constitution of a number of choline derivatives; both papers gave impetus to later studies of great importance to neurology. Chemotherapy was made definitive by the discovery of salvarsan in 1909 by Ehrlich and Hata, announced in a publication from Berlin (1910).

1911–1920

The second decade of the century opened with the publication of the paper by Noguchi on the cultivation of *Treponema pallidum*, the only communication of the year 1911 of vital importance to neurology. The next year, however, produced a long list, including Ehrlich's introduction of neoarsphenamine and Alfred Hauptmann's discovery of the effect of luminal (phenobarbital) on epilepsy, two therapeutic aids of great value. In clinical neurology, Kinnear Wilson described in detail progressive familial lenticular degeneration, first noted by Frerichs in 1861; Schilder delineated encephalitis periaxialis diffusa; Leonard P. Mark gave an account of his personal experience with acromegaly and Legge and Goadby wrote a full account of lead poisoning and lead absorption. Alfred E. Frank associated the posterior lobe of the pituitary with diabetes insipidus and Cushing, calling on his by then large experimental and clinical experience with pituitary disorders, published his monograph, "The Pituitary Body and its Disorders." Acknowledged as the most important medical book of the decade, it proved to be one of the outstanding contributions of American neurology. In it he described his new surgical method, contrasting the intracranial approach with the endonasal routes of Schloffer and Hirsch (1911).

In 1913 Noguchi and Moore obtained a pure culture of *Treponema pallidum* from the brains of patients with general paralysis, thus giving proof of Fournier's statistical assumption of 1894 and Wassermann's findings of a positive test in the cerebrospinal fluid of persons with paresis (1906). Lange described his colloidal gold reaction in the same year. Flexner, continuing his work on poliomyelitis virus, was able, with Lewis, to produce the disease with the twentieth generation of the cultivated organism.

Morris Simmonds described a fatal cachexia of hypophyseal origin, since known as "Simmonds' disease," in 1914; Walter E. Dandy and Kenneth D. Blackfan produced experimental hydrocephalus; and J. J. Déjérine completed his excellent textbook on "Semiologie des affections du système nerveux" (Paris, 1914). In the same year, H. H. Dale demonstrated the inhibitory action on the heart of acetylcholine and A. J. Ewins isolated acetylcholine from ergot, both reports leading up to Loewi's humoral-transmission experiments of ten years later.

Only one event seems worthy of record in 1915. Smith Ely Jelliffe and W. A. White published their outstanding textbook "Diseases of the Nervous System."

Studies of war injuries and diseases were soon forthcoming. The best of these was Jules Tinel's "Les blessures des nerfs" (Paris, 1916), shortly translated into English and widely used during the war by English and American medical officers. Louis H. Weed, in America, established the circulation of the cerebrospinal fluid, mapped out its pathways and disclosed its points of entrance to and exit from the subarachnoid space. His fundamental studies were further extended in 1917. Jakob Erdheim described pituitary dwarfism; Villaret, his retroparotid syndrome. W. H. Gaskell summarized his long researches on the histology of the autonomic nervous system in a book of permanent value.

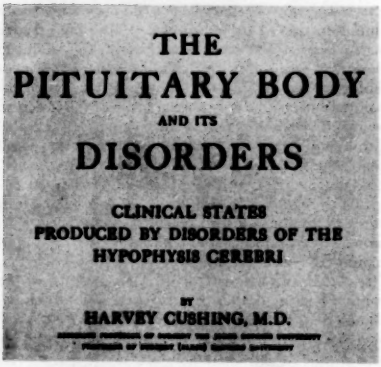

FIGURE 3. *Harvey Cushing on "Pituitary Body and Its Disorder" (1912).*

In 1917 Henry Head and George Riddoch published their wartime study on injuries to the spinal cord, depicting the automatic bladder and excessive sweating — a classic study. Riddoch shortly thereafter published his description of the effects of complete transection of the spinal cord in man. These two papers were the result of painstaking study of wounded soldiers. In neurosurgery, Cushing described "Tumors of the Nervus Acusticus and the Syndrome of the Cerebello-pontile Angle," thus defining a group of brain tumors long unclassified and only partly recognized. Economo, quick to recognize a newly widespread disease, gave the first full description of encephalitis lethargica, then seen in Austria but soon to be noted around the world. The same year an important book was published posthumously: "The Conduction of the Nervous Impulse," by the gifted physiologist Keith Lucas, who had died in 1916.

Studies on acetylcholine were continued by Reid Hunt, who demonstrated that tissues were more sensitive to this drug after previous treatment with physostigmine. In clinical neurology, a landmark was erected by Wagner-Jauregg, who in 1917 returned to his idea of inoculating persons with paresis with malaria to induce pyrexia, first proposed by him in 1887. His paper, "Über die Einwirkung der Malaria auf die progressive Paralyse," was published in 1918–1919.

With the termination of the war, some of the most important discoveries of the modern period followed in quick succession. Walter E. Dandy injected air into the cerebral ventricles, introducing the subject now known as ventriculography; he also introduced the technic of pneumoencephalography by means of the injection of air into the spinal canal. Cecile and Oskar Vogt described the syndrome of the corpora striata in 1919–1920.

1921–1930

In 1921 Jean Sicard and Jacques Forestier opened an entirely new field of diagnostic investigation with the use of lipiodol, an iodized poppy-seed oil, as a contrast medium in the spinal canal. This method, with various modifications, proved to be of great value in the localization of spinal-cord tumors and ruptured intervertebral discs. In the same year, J. N. Langley extended the work of Gaskell and others on the autonomic nervous system, dividing it into units and bringing some order to the complexities of the efferent system of nerves. Of greater importance, however, was the establishment of the humoral theory of chemical transmission of nerve impulses at the synapse by Otto Loewi in a series of papers (1921 to 1926). Also in 1921, Karl Spiro and August Stoll isolated ergotamine and Frederick Tilney and H. A. Riley published a splendid summary of our knowledge of the form and functions of the central nervous system.

In 1924 Loewi, with Navratil, established the presence of cholinesterase, the catalytic agent causing hydrolysis of acetylcholine and its inhibition *in vitro* by physostigmine. At the same time Joseph Erlanger and H. S. Gasser disclosed the action currents of nerves by means of the cathode-ray oscillograph, and E. G. T. Liddell and C. S. Sherrington described the myotatic, or stretch, reflex.

J. B. Collip and D. B. Leitch used parathyroid hormone in the treatment of tetany in 1925, Collip having isolated parathormone in the same year.

Two volumes of fundamental studies were published in 1926. Percival Bailey and Harvey Cushing classified the glioma group of brain tumors on

a histogenetic basis and correlated their study with prognosis. This pioneer investigation led to a reorientation of brain-tumor pathology and to the method of histologic diagnosis from biopsy specimens at the time of operation. In the same year Henry Head issued his study on "Aphasia and Kindred Disorders of Speech," a landmark in the history of the subject.

Another diagnostic contribution, in addition to ventriculography, pneumoencephalography and lipiodol injection, was made in 1927 when the Portuguese neurologist Egas Moniz presented a paper on arterial encephalography, particularly important in the localization of brain tumors. From Joszef Baló of Budapest came the description of a rare form of encephalitis, periaxialis concentrica, described as chiefly affecting the white matter, in contrast to Schilder's diffuse type (described in 1912).

The Japanese form of epidemic encephalitis was delineated by Kaneko and Aoki in 1928, differing from Economo's lethargic encephalitis (as studied in 1917). Pavlov's lectures on conditioned reflexes were issued in English from 1928 to 1942. At the same time Alexander Fleming, a bacteriologist, noted the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of the organism of influenza, in a paper published in 1929. This laboratory aid passed almost unnoticed until Ernest Chain and his associates isolated penicillin and used it as a chemotherapeutic agent in 1940.

The decade closed with Harriet Edgeworth's description of her personal experience with the use of ephedrine in the treatment of myasthenia gravis.

1931–1940

W. B. Cannon, with Bacq, gave renewed impetus in 1931 to the theory of the humoral transmission of the nerve impulses when he disclosed the action of the hormone "sympathin" on smooth muscle. At the same time, Erich Engelhart gave further proof of the action of acetylcholine on voluntary musculature and O. W. Gibbs, with Szelöczey, produced the same chemical compound by stimulating the chorda tympani nerve (1932). In 1932 also, LeGros Clark disclosed some of the finer anatomic connections of the thalamus in man. He later studied those of the hypothalamic nuclei (1936). In neurosurgery, Harvey Cushing completed his monograph on "Intracranial Tumors," a publication giving a summary of his vast experience in the treatment of over 2000 cases. Remen gave a hint of the value of neostigmine in the treatment of myasthenia gravis but failed to pursue the subject. It was left to Walker to introduce the modern treatment to the world (1934).

In 1933 R. S. Mackenfuss, with Charles Armstrong and H. A. McCordock, isolated the virus of encephalitis of the St. Louis type in 1933; Cannon and Rosenblueth separated adrenalin from sympathin and Wilhelm Feldberg and Gaddum demonstrated that acetylcholine was the chemical transmitter in the sympathetic ganglion.

The outstanding paper of 1934 was the communication by Mary B. Walker on the remarkable effects of physostigmine on myasthenia gravis, soon followed by the use of Neostigmine (Prostigmine) by the same author (1935) in treatment and by Viets and Schwab as a diagnostic test (1935). In the same year Laurent and Walther noted the favorable effect of potassium salts on myasthenia gravis.

The autonomic nervous system was fully considered by J. C. White in 1935, with particular emphasis on the value of surgical interruption for pain and other disorders. With creditable thoroughness, Oswald Bumke and Otfried Förster issued a "Handbuch der Neurologie" in seventeen volumes (1935–1937), one of the most important publications in the fifty years from 1901 to 1950. However, 1935 should not be surveyed without mention of the paper by Gerhard Domagk introducing "prontosil," the first of the sulfonamides, which was to revolutionize the treatment of bacterial infections, including those of the nervous system, such as meningitis. Soon the meningitis of World War I was to become only a historic memory.

Berger's "brain waves" of 1929, re-emphasized by their demonstration in man by Adrian and Matthews (1934), were put to clinical use by Grey Walter in 1936, when he used them as aids in the localization of brain tumors.

The most important book of 1938 was J. F. Fulton's "Physiology of the Nervous System." This book, with its subsequent editions, has become a standard text throughout the world. A. E. Walker published "The Primate Thalamus" in the same year.

In 1940 the outstanding book of the decade was published: the two-volume "Neurology" by S. A. Kinnear Wilson; it was edited by A. N. Bruce, for Wilson had died in 1937. It can only be compared for completeness with Oppenheim's "Lehrbuch" of 1894 and Gowers' "Manual" of 1886–1888. They are the three greatest textbooks in neurology. The year 1940 also saw the rapid development of the sulfonamides, with Long's "sulfathiazole," Marshall's "sulfaguanidine" and Roblin's "sulfadiazine." Of even greater importance, however, was the isolation of penicillin as a chemotherapeutic agent by Ernest Chain and his associates.

1941–1950

To review the reported research published during the last decade in a systematic manner, year by year, is not possible. Much of the work is fragmentary and incomplete; it cannot be fully evaluated at the present time. Moreover, there is evidence of a change in the reporting of scientific advances. Specific papers that can be dated are no longer the

rule. The current method of publication is a series of papers revolving about a single item of research. Advancements are now reported largely in piecemeal style little by little; dating by year is no longer possible, in many instances, except perhaps to indicate the beginning of a trend. For instance, Paul Weiss has carried on a long series of researches into the embryologic factors in the growth of the peripheral and central nervous systems. His earliest work may be dated about 1924, but much of it has been done since 1941. Fortunately, a summary of his contributions has appeared in book form: "Genetic Neurology: Problems of the Development, Growth, and Regeneration of the Nervous System and its Function" (1950). The First International Conference on the Development, Growth, and Regeneration of the Nervous System, held in 1949, marks the date of the birth of a new biologic discipline, "genetic neurology." Wilder Penfield and his research group in Montreal have contributed continuously to the data on epilepsy and cerebral localization. In 1941 Penfield, with Erickson, summarized his researches, but since then important additions have been made, including a paper by Penfield and Steelman (1947) on the treatment of focal epilepsy by cortical excision. In like manner, R. S. Snider began a series of investigations of the cerebellum in 1942 in which he demonstrated tactile, auditory and visual areas. His researches have made it necessary to abandon the old concepts of a cerebellum functioning as a whole and only in the proprioceptive sphere (1950).

Since the stimulation given to the development of anticonvulsants by Putnam and Merritt (1937), at least nine drugs have been developed and are in current use in 1950. In 1948 E. L. Gibbs and F. A. Gibbs, with Fuster, defined psychomotor epilepsy as a specific epileptic syndrome with a focus of electroencephalographic activity in the anterior portion of the temporal lobe.

Howe and Bodian advanced the study of poliomyelitis in a monograph, "Neural Mechanisms in Poliomyelitis" (1942). The histopathology of infantile paralysis (particularly the bulbar type) was investigated thoroughly by A. B. Baker. The study was correlated with research on the medullary functions disturbed by this disease. These important investigations were still being reported on in 1950. The First International Poliomyelitis Conference met in 1948 and published its valuable "Transactions" in 1949.

In 1947 it was found that tractotomy of the bulbospinal tract of the trigeminus, as advocated by Sjöqvist in 1938, would also relieve the geniculate neuralgia of Ramsay Hunt as well as the pain associated with disorders of the ninth and tenth nerves.

The development of our knowledge of the importance of the ruptured intervertebral disk was summarized by Mixter in 1949, twenty years after Dandy had discovered this lesion without fully recognizing its significance. The syndrome was defined by Mixter and Barr in 1934.

A few events may be more definitely dated. In 1941, for instance, John H. Talbott published his paper on periodic paralysis, demonstrating the constant finding of a decrease in concentration of serum potassium during attacks. The same year C. and O. Vogt issued their "Thalamusstudien."

In 1942 Freeman and Watts wrote "Psychosurgery," a report on their experiences with the operation first devised by Egas Moniz in 1935. In 1943 "Die Multiple Sklerose des Menschen" by Georg Schaltenbrand was published in Germany; this study has not yet been fully evaluated.

With the close of hostilities of World War II, publications came out more rapidly. Fulton's "Harvey Cushing" (1946) led the field in neurologic biography; Benda explored the little-known field of "Mongolism and Cretinism" (1946); a monumental "Bibliography of Infantile Paralysis, 1789-1944" (1946) was edited for the National Foundation for Infantile Paralysis by Morris Fishbein; Gustave Roussy issued his "Traité de Neuro-endocrinologie" (1946).

Two publishing events of 1947 were of importance: The most influential book of the past fifty years in neurophysiology, "The Integrative Action of the Nervous System," by Sir Charles S. Sherrington (first published in 1906), was reissued, with a new preface by the author, and "Clinical Neuro-ophthalmology" was published by F. B Walsh.

Donald Munro carried out a long and important series of investigations on spinal-cord injuries and their treatment; Selverstone and his associates disclosed brain tumors with radioactive phosphate and Loyal Davis revealed them by means of di-iodofluorescein. By 1950 even ultrasonic technics were being used for cerebral localization.

In 1949 Krabbe, who had continued his studies on brain degeneration, described an infantile type of poliodystrophia cerebri progressiva, characterized by extensive wasting of the gray matter and preservation of the white matter. He had described the opposite condition, now known as leukodystrophia, in 1916.

The Fourth International Neurological Congress was held in Paris in 1949, with a large attendance of clinical and research workers. Investigation of exceptionally high caliber was reported, indicating a growing interest in the subject following the somewhat dormant period of the 'thirties and early 'forties.

Summary

Much of the specific practice of neurology has been entirely changed in this fifty-year period. In Putnam's day syphilis and tuberculosis were two of the principal causes of diseases of the nervous system. At the present time, neither occupies much of the neurologist's practice. Indeed, arsphenamine, tryparsamide and penicillin have

caused tabes dorsalis, common in 1900, to become a rarity. Gone, too, are mastoiditis, temporal-lobe abscess, the pyogenic forms of meningitis and the nervous manifestations of typhoid fever, pneumonia, smallpox and a host of other diseases that used to fill the hospital beds at the turn of the century. There has been, moreover, a change in hospital practice. Although the out-patient clinic still continues as the center for the study and evaluations of ambulatory patients, patients in hospital beds now provide the chief source of clinical research. In addition, the department of neurology is now as a rule closely integrated with the section on neurosurgery and is often separated entirely, in the physical sense, from psychiatry. New drugs have brought many changes, as, for instance, neostigmine in myasthenia gravis, dilantin in epilepsy, the sulfonamides and the antibiotics. The neurologist today must know a great deal about blood chemistry, fluid balance, oxygen pressure and other subjects far removed from the thinking of Putnam in 1901. A closer relation with general medicine has been developed, but the outstanding features of the past half-century are the integration of laboratory research with clinical practice, the development of diagnostic aids such as myelography, electroencephalography, pneumoencephalography and others, and the growth of neurosurgery. Little progress has been made in the treatment of the degenerative diseases of the nervous system, as is the case with degenerative conditions elsewhere in the body. Diseases due to viruses are still unconquered, but the next fifty years may well see the disappearance of viral as well as degenerative diseases. Such an accomplishment would be no greater than the advance we have witnessed since 1901.

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CASE 37111

Presentation of Case

A thirty-eight-year-old woman was admitted to the hospital because of headaches, vomiting and mental confusion.

The first deviation from previously normal health occurred about seven years before admission, when, two weeks after the uneventful delivery of her second child, lactation ceased spontaneously. The menstrual periods, previously fairly regular, then failed to return, and the amenorrhea persisted to the time of admission. Over the following few years the axillary and pubic hair became scanty, the scalp hair became drier and thinner and the breasts became smaller and the areolae lighter in color; she gained about ten pounds despite unchanged appetite, and she gradually lost all sexual desire. About three years before admission, she began to be unusually drowsy, although she was still able to carry on her daily activities. She began to have occasional episodes of severe frontal and occipital headaches lasting several days, unaccompanied by any other known symptoms. She had had a blow on the head at about the time the headaches and drowsiness began, but it was not severe and was not accompanied by any loss of consciousness; it is uncertain whether it preceded or followed the development of these symptoms. In the following year she became apathetic, recent memory became impaired, and she underwent an otherwise undescribed personality change that resulted in her admission to a state mental hospital about two and a half years before entry. While there she had an attack of vomiting and then became unconscious and incontinent for twenty-four hours, with some stiffness of the neck, bilaterally hyperactive tendon reflexes and extensor plantar reflexes. This episode was followed by occipital headaches and "dizziness." A ventriculogram done at this time was reported to show symmetrical dilatation of the lateral, third and fourth ventricles. The patient was given thyroid extract and dilantin. In the ensuing weeks the headaches and dizziness subsided, and she became alert, neat and cheerful. She returned home after about one year of hospitalization.

Seven months before admission, after having been in reasonably good health in the meantime, she entered another hospital because of occipital headaches, mental confusion and vomiting without nausea. She stated that she had been taking about 0.7 gm. of dilantin daily. On examination she was incoherent and poorly responsive; she had bilateral extensor plantar reflexes but no other abnormal physical findings. X-ray films of the skull showed intracranial calcification above and a little to the left of the sella turcica, whereas the sella and clinoid processes were reported as normal. Dilantin was omitted, and she was kept under observation for about three weeks, during which time she improved steadily. She seemed fairly well when discharged home.

While at home, she had periodic episodes of apathy and lack of interest in her surroundings. She took thyroid extract regularly without any apparent benefit. For several months she had recurrent severe occipital headaches, occasionally with precipitous vomiting. Ten days before admission she entered another hospital in a state of apathy and drowsy confusion. While there, she had a peculiar attack characterized by generalized fine tremors throughout the body, without loss of consciousness, that persisted for three days. Studies at the other hospital, which were very thorough, included an eosinophil count of 560 that rose to 600 after administration of 0.3 cc. of 1:1000 epinephrine; the eosinophil count fell from 600 to 420 four hours after a test dose of 25 mg. of ACTH (adrenocorticotrophic hormone).

On physical examination the patient was well developed and well nourished but lethargic, apathetic and disoriented as to time and place. She was incontinent of urine and feces. The skin was smooth and dry, the scalp hair fine and dry but normally abundant and the axillary and pubic hair scanty. The breasts were atrophic. There was bilateral pes cavus. There were frequent irregular, purposeless movements of the limbs and at times a fine generalized tremor. Visual acuity was seemingly unimpaired. The optic fundi were normal. Visual fields were thought to be normal, but the patient's inattentiveness prevented adequate testing. The other cranial nerves were unremarkable. There was no muscular weakness, and no sensory impairment to pinpricks. Tendon reflexes were generally increased; there were bilateral extensor plantar reflexes. The heart, lungs and abdomen were normal.

The temperature was 99.0°F., the pulse 60 and the respirations 20. The blood pressure was 110 systolic, 70 diastolic.

Routine blood count and urinalysis were normal; the urine Sulkowitch (calcium) test was ++. On lumbar puncture the fluid was clear and colorless, was under an initial pressure equivalent to 380 mm. of water, contained 4 lymphocytes and 51 mg. per 100 cc. of protein and gave a negative gold-sol and Wassermann test. The fasting blood sugar was 110 mg., the calcium 10.2 mg., the phosphorus 3.0 mg. per 100 cc., the alkaline phosphatase 3.0 units, the nonprotein nitrogen 18, the total protein 6.94 gm., the albumin 3.77 gm. and the globulin 3.17 gm. per 100 cc. The sodium was 129, the chloride 104, the carbon dioxide 26.2 and the potassium 3.8 milliequiv. per liter. The prothrombin time was 20 seconds (normal, 17 seconds). A urine FSH (follicle-stimulating hormone) test was negative for 6.5, 13 and 52 mouse units per twenty-four hours. The urine creatinine-uric acid — ratio was 1.8 (control specimen, 2.0). Three days later the sodium was 136.5, the chloride 105 and the carbon dioxide

FIGURE 1. *X-ray Film of Skull.*

24.2 milliequiv. per liter. An electroencephalogram showed generally increased voltages and bilateral slow wave activity (4, 5 and 6 per second and some 2 to 3 per second), least marked in occipital leads. X-ray films of the chest were normal. Plain films of the skull showed some amorphous calcification in the region just above and on either side of the sella turcica, some of which was thought to be within the sella itself. The tips of the posterior clinoid processes were bent slightly forward. Another calcification was seen slightly to the right of the midline somewhat below and posterior to the region normally occupied by the pineal body (Fig. 1).

The patient's condition remained unchanged for four days. On the fifth hospital day she became comatose, and responded only to painful stimuli. It was thought at this time that there was early papilledema on the left. The pupils were equal and small and reacted slightly to light. The limbs were held in extensor rigidity. On puncture of the left lateral ventricle, the cerebrospinal fluid was under

an initial pressure equivalent to 240 mm. of water, which fell to 60 mm. after removal of 20 cc. of fluid. The cerebrospinal fluid contained 9 mg. per 100 cc. of protein. Ventriculograms via the left lateral ventricle showed dilatation of the lateral ventricles, more marked on the left. The right temporal horn was dilated but not displaced; the left temporal horn was not well seen. No air was seen in the third or fourth ventricle. On the following morning an operation was performed.

Differential Diagnosis

Dr. Alfred O. Ludwig*: Would you show us the x-ray films, Dr. Wyman?

Dr. Stanley M. Wyman: The x-ray films of the chest taken with the patient in the supine position show no gross abnormalities. The plain films of the skull demonstrate this faint, hazy calcification in and about the region of the sella turcica, rising above it in a somewhat arcuate manner anteriorly and rising just above the posterior clinoid processes, which are definitely thinned and possibly bent forward. The small calcification described posteriorly may be this small shadow, but I am not too certain of that.

Dr. Ludwig: Could that shadow be the displaced pineal body?

Dr. Wyman: I cannot identify it in the other projections. I think it is a dubious finding.

Air studies made with a catheter in the left lateral ventricle show rather asymmetrical filling of the lateral ventricles, the left, as seen in the posteroanterior film, being larger than the right. This is also confirmed in the anteroposterior projection. This may be due to the manner of filling, however. There is no definite encroachment on the visualized portion of the lateral ventricles. The right temporal horn is well seen and is large. The left horn cannot be seen with certainty. I think there is one additional point about the sella turcica. There seems to be asymmetry of the floor; the left portion of the sella floor, as seen in this view, lies lower than its corresponding portion on the right, suggesting the definite possibility of something within the sella.

Dr. Ludwig: Was the optic chiasm examined?

Dr. Wyman: No.

Dr. Henry R. Viets: Can you see the fourth ventricle?

Dr. Wyman: I cannot be sure of it, Dr. Viets.

Dr. Ludwig: In summary, the history gives evidence of the presence of a hypopituitary syndrome, eventual episodes of increased intracranial pressure and a psychosis, unfortunately not very well described, suggesting that the disease was probably somewhere within the cranial cavity. It is of interest that this woman's symptoms began shortly post partum. This may be coincidental, to be sure. However, it makes one think of panhypopituitarism, which often begins after pregnancy. The first symptoms of what I consider a fairly obvious hypopituitary syndrome were the genital dystrophy, the amenorrhea, the changes in axillary and pubic hair, the atrophy of the breasts, the suppression of lactation and the slight gain in weight. A point was borught into the history that may or may not be important: namely, that she had had a head injury of some sort. Head injury makes one think of the possibility of a subdural hematoma, although many of the other symptoms, particularly those of hypopituitarism, could not be explained on that basis. This was followed by the poorly described personality change, which must have been fairly severe, or else the patient would not have been admitted to a mental hospital. I cannot deduce from the description either the nature or the cause of this disturbance. I cannot tell whether or not it was a so-called functional psychosis — manic-depressive or schizophrenic, — a toxic psychosis or an organic psychosis.

In regard to the personality changes that occur secondarily to intracranial neoplasm, the area with which these are most frequently associated is the frontal lobe. That psychosis is usually characterized by lack of interest and a loss of normal emotional lability — the patient no longer cares or worries, and nothing interests her. This is much like the syndrome that is seen in many lobotomized patients. Frequently associated with tumors in this area are slovenliness in dress and habits, obscurity of speech, facetiousness — so-called Witzelsucht — and loss of memory for recent events. Personality changes are also described with tumors in the region of the hypothalamus and the third ventricle. The descriptions in the literature stress the appearance of euphoric or manic symptoms in this syndrome. Such symptoms have also been noted in the presence of suprasellar cysts. These patients are disoriented, have increased irritability and are argumentative. Sometimes, depending on the location of the lesion, they may have autonomic fits, either sympathetic or parasympathetic in nature. Apparently, however, this patient recovered from the psychotic episode.

At one time while in the hospital she apparently had a sudden increase in intracranial pressure, which caused vomiting, unconsciousness, incontinence and some extrapyramidal signs, with extensor plantar reflexes and stiffness of the neck. The stiffness of the neck, the reflex changes and the dizziness can probably be explained by cerebellar dysfunction secondary to pressure. I cannot explain why this patient was given thyroid extract and dilantin, but I wonder if this had anything to do with the improvement. The episodes apparently lessened spontaneously, as well.

Seven months before admission she entered another hospital because of an episode of headache, confusion and vomiting, and at that time was taking a fairly large amount of dilantin. This in itself may

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produce some drowsiness, but I do not believe one can ascribe all her symptoms to this drug. Again she improved, possibly due in part to the omission of dilantin. I feel very strongly that the symptomatology in this patient, as well as the x-ray findings and what I believe to have been episodes of intermittent increased intracranial pressure, all point to the presence of an intracranial tumor of some sort.

The laboratory findings really do not help me much in establishing a diagnosis. There was a very slight discrepancy in the albumin-globulin ratio — the albumin was somewhat low and the globulin somewhat high. There was certainly increased cerebrospinal-fluid pressure. The protein of the spinal fluid was only slightly elevated. The negative FSH test is what one would expect in any form of hypopituitarism. The changes in the eosinophil count following the administration of ACTH were probably within normal limits.

If this was an intracranial tumor, or if there was increased intracranial pressure, what was the cause of it? The presence of calcification in the region of the sella draws my attention to that area. I would think first of a suprasellar cyst, or a so-called craniopharyngioma, as possibly explaining the symptoms. These occur in that area. They produce calcification; 85 per cent of them show some evidence of calcification on x-ray examination. They constitute some 5 per cent of all cerebral tumors. They may give rise by secondary pressure to the hypopituitary syndrome that was present in this woman. By occluding the third ventricle they often give rise to some degree of dilatation of the other ventricles and increased intracranial pressure, as well as to certain secondary cerebellar signs. Craniopharyngiomas are usually found in childhood, but they do occur in adults.

What other types of calcifying tumors occur in this region? Meningiomas may occur. Usually they result in some hyperostosis of the sella turcica and are not ordinarily associated with hypopituitarism. There is no x-ray evidence to lead one to suspect that a meningioma of that sort was present. Unfortunately, one very important corroborating sign, bitemporal hemianopsia, was missing here. Obviously the patient was sufficiently disoriented and inattentive so that satisfactory examination of the visual fields could not be made.

Another possibility is glioma of the optic chiasm. Nearly all gliomas of the optic chiasm are found in childhood and give rise to a dilated optic foramen, of which there is no evidence here. Teratomas also occur in this area. One should also consider a tumor of the pituitary gland itself. Although the changes in the sella turcica that Dr. Wyman has described to us may point to the origin of the tumor from the anterior portion of the pituitary gland, the sella turcica is ordinarily far more ballooned with such tumors than it was in this case.

Are there any other possibilities that should be considered? One should certainly think of a frontal-lobe tumor, but it would be difficult to explain the presence of the hypopituitarism on the basis of a frontal-lobe tumor unless a considerable degree of extension had taken place. The episodes of intermittent increase in cerebrospinal-fluid pressure also suggest the possibility of an intraventricular tumor that acted as a ball valve, shutting off the circulation of the ventricles and causing sudden increase in pressure. These are usually colloid cysts or papillomas of the choroid plexuses. They are very rare, and usually occur in children. The visualization of the ventricles in the x-ray films shows no evidence that any such tumor was present. The dilatation of the ventricles alone might lead one to suspect the rather rare condition of arachnoiditis of the ventricles and of the aqueduct, leading to the occlusion of the aqueduct and internal hydrocephalus, but the presence of calcification would rule this out. I remember having seen such a case in the past, but I do not consider it the correct diagnosis in this case.

Finally, cerebral tumors may be metastatic. In this area, with the calcification and with the signs that are present, I would be very much surprised if a metastatic tumor was found. I shall make my final diagnosis intracranial tumor, probably craniopharyngioma, with secondary hypopituitary syndrome, increased intracranial pressure and internal hydrocephalus.

Dr. Viets: This is still a puzzling case to me. I think the point that should be emphasized is that the patient had been sick for seven years prior to operation. Amenorrhea was the first symptom; its persistence indicated that there was pituitary dysfunction but not necessarily actual disease. I am unhappy about the localization of that lesion, partly because if it was a suprasellar cyst I should expect it to have disclosed itself even more definitely in the seven-year period and not to have led to intermittent symptoms such as she exhibited. Moreover, the fourth ventricle was described as enlarged at the initial examination. If it was enlarged, certainly the blocking of the ventricular pathway was not at the level of the pituitary but must have been lower in the posterior fossa. A posterior-fossa lesion would explain the variation in symptoms for over seven years and the bilateral character of the enlarged ventricles; it is also an adequate cause for secondary pituitary dysfunction.

Dr. Benjamin Castleman: Dr. Bartter, would you tell us the opinion on the ward?

Dr. Frederic C. Bartter: We had very little time to study the endocrine status. A specimen for an FSH test was collected but had not been reported when the decision had to be made. The amenorrhea might indicate hypopituitarism, but there was very little else to support it. She had stopped lactating after two weeks, but that is not

unusual in normal women. What we had to decide was whether the basis of her crises was chemical or intracranial. She was scheduled to go to the Thyroid Clinic at 2:00 p.m. At noon she was well, but by 2:00 p.m. she was in deep coma. At that time it seemed quite clear that there was intracranial disease and that it was not a chemical Addisonian crisis, so she was transferred to the Neurosurgical Service. When she was in deep coma we were able to see her eye grounds well for the first time; there seemed to be papilledema on one side and optic atrophy on the other. All in all, the symptomatology appeared to us to fit best with suprasellar cyst.

DR. JACOB LERMAN: I saw this patient once briefly. I think the opinion at that time was that she did not have the characteristic picture of panhypopituitarism. She had evidence of FSH dysfunction but very little else. The chemical determinations seemed to bear this out. We were unable to do any studies of metabolism or of radioactive-iodine uptake. Our general impression was that the tumor war a suprasellar cyst.

DR. BARTTER: I expect that you found very little in the pituitary or adrenal gland.

CLINICAL DIAGNOSIS

Suprasellar cyst.

DR. LUDWIG'S DIAGNOSES

Suprasellar tumor, ?craniopharyngioma.
Secondary hypopituitary syndrome.
Internal hydrocephalus.

ANATOMICAL DIAGNOSIS

Craniopharyngioma, suprasellar (adamantinoma).

PATHOLOGICAL DISCUSSION

DR. EDWARD P. RICHARDSON, JR.: The operation described in the record was an incision through the left frontal cortex to enter the anterior portion of the left lateral ventricle. The ventricle appeared somewhat large, as you saw in the x-ray films. The foramen of Monro could easily be visualized, and the surgeon attempted to explore the foramen in order to see the third ventricle. When he did so, there was an immediate copious gush of rather viscous brownish fluid. Some of this was collected; on examination it showed a small amount of blood and a few macrophages but no cholesterol crystals. Apparently a cyst wall had been punctured in the foramen of Monro, but on further exploration no cyst wall could be seen. The surgeon got what he thought was an adequate view of the third ventricle and saw no lesion in it. Nothing further was done surgically, and the patient was returned to the ward. She never recovered consciousness, had bouts of extensor rigidity and a mounting temperature and died six days after the operation.

As Dr. Ludwig predicted, a craniopharyngioma was found. The tumor mass was round, somewhat irregular in its contour, yellowish and very firm, with extensive calcification in its walls. It occupied the exact position of the pituitary stalk, none of which could be seen. Anterior to it lay the optic chiasm and posteriorly the two mammillary bodies, these structures being somewhat compressed but not destroyed. Beneath it, within the sella turcica, was the pituitary gland, which was intact although compressed and flattened. Section of the tumor showed it to be a cyst containing partly calcified debris. Within the third ventricle lay a membrane-like structure that was continuous with the wall of the suprasellar cyst (Fig. 2). It seems likely that during life and before operation there was a large cyst, of which this membrane was the remnant, that bulged upward into the third ventricle and produced obstruction of the ventricular system at the foramina of Monro. It was undoubtedly this cyst that the surgeon punctured during the exploration.

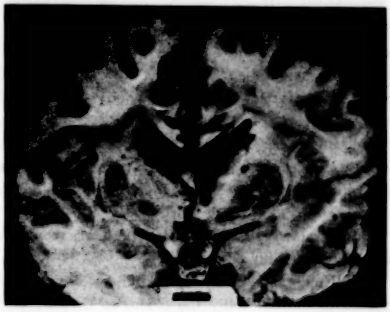

FIGURE 2. *Gross Section of Brain Showing Suprasellar Craniopharyngioma.*
Arrow indicates membrane in third ventricle.

Histologically, the tumor was typical of the usual craniopharyngioma. It is an epithelial structure in which one finds epithelium like that normally found in the oral cavity. Much of the material in the center of the tumor consisted of partly calcified squamous debris. In addition, there were small areas within the wall that resembled the dental-enamel organ in the developing embryo. Perhaps one can also classify the tumor as an adamantinoma (or ameloblastoma). The pituitary was histologically intact. There was plenty of perfectly sound-looking anterior-lobe tissue.

DR. BENJAMIN CASTLEMAN: I think one of the interesting points about this case is how pressure on the anterior lobe could produce at least some of the signs of panhypopituitarism. According to Sheehan, about 95 per cent of the pituitary tissue

has to be destroyed before a true Sheehan's disease occurs. It must mean that some of the tracts were compressed and that this produced the signs and symptoms of hypopituitarism.

DR. BENEDICT: If you operate on a suprasellar cyst soon enough, can you cure it by surgery?

DR. RICHARDSON: They have been cured by surgery when they were not too large. With respect to the bouts of increased intracranial pressure, it seems very likely that the cyst, when intact, may have acted in a ball-valve manner.

DR. VIETS: There is one important sign that was not included: atrophy of one optic nerve. Had I known that, I should have been much more certain of Dr. Ludwig's diagnosis.

DR. RICHARDSON: Not everybody agreed with that finding.

DR. BARTTER: I asked Dr. Robert S. Schwab to look at the eye grounds; he agreed that there was atrophy of one optic nerve and blurring or edema of the other.

DR. WYMAN: I think that the appearance of the sella turcica is important, too.

DR. CASTLEMAN: Unfortunately we were permitted to examine only the brain, so that we have no information about the other endocrine glands.

CASE 37112

PRESENTATION OF CASE

A sixty-five-year-old woman was brought to the hospital in an unconscious state.

The patient had enjoyed relatively good health until two years before admission, when it became known that she had hypertension. She received digitalis daily and ammonium-chloride medication occasionally but no mercurial diuretics. No orthopnea or pain had been reported, although slight exertional dyspnea and moderate ankle edema were noted. For one year there were episodes of "spasms" characterized by a feeling of shakiness, with some inco-ordination. On the night before admission she complained of slight pain and stiffness at the back of the neck, but this was considered of no significance. Throughout the next day she seemed quite well. In the evening, while preparing dinner, she suddenly slumped into a chair, called out her son's name and became completely unresponsive. She was immediately brought into the Emergency Ward.

Physical examination showed a pale, obese woman with cold, clammy extremities and Cheyne–Stokes respirations. The pulse was regular, faint in the left wrist, and unobtainable in the right. The neck veins were flat. The blood pressure was barely perceptible, with a reading of 65 systolic, 50 diastolic on the left and 0 systolic, 0 diastolic on the right arm. The left cardiac border was 13 cm. from the midsternal line in the fifth intercostal space. The sounds were of good quality, without audible murmurs; occasional extrasystoles were present. The chest was symmetrical and resonant to percussion, with scattered moist rales throughout. The abdomen was obese, obscuring satisfactory palpation, but no tenderness or splinting was present. Procidentia with cervical ulceration and accompanying abundant foul leukorrhea were observed. Rectal examination was negative. There was bilateral divergent strabismus, round, equal pupils and absent corneal reflexes. Although equal hypoactive biceps and triceps jerks were present, knee and ankle jerks were areflexic and plantar reflexes were absent. Extremities were flaccid and immobile.

The urine was acid and cloudy, with a specific gravity of 1.015, a ++ test for albumin and a negative reaction for sugar and bile; the sediment contained many white cells and abundant bacteria per high-power field. Examination of the blood showed a hemoglobin of 11.0 gm. and a white-cell count of 19,950, with 89 per cent neutrophils and normal platelets. A stool was guaiac negative. The cerebrospinal-fluid pressure was equivalent to 120 mm. of water before and after removal of 8 cc. of clear, colorless, Pandy-negative fluid. The electrocardiogram showed no gross abnormality.

The patient remained comatose. More rales developed in the chest and the neck veins became distended — more markedly on the right. Intravenous therapy of 10 per cent dextrose in water was begun. There were bilateral extensor plantar responses prior to death, which occurred quietly fourteen hours after entry.

DIFFERENTIAL DIAGNOSIS

DR. ROBERT BERG*: The outstanding finding in this case was the sudden development of unconsciousness. Unconsciousness of such acute onset is really

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rather uncommon, and I think it provides the neatest point of departure for outlining the differential possibilities. First of all, I might dispose of some conditions that obviously were not the basis for the illness. For example, drug intoxication may be ruled out, although anybody who reads the usual literature available on the newsstands must think of cyanide poisoning. We do not often think of poisonings and I am sure it is not necessary to do so here. The only other drug poisoning might be from ACTH (adrenocorticotrophic hormone). ACTH can apparently do anything — at least, I am told so by the fourth-year students and the house officers. If it can do anything, it might cause this. As a matter of fact, we have had one or two instances in which there was sudden unresponsiveness that was apparently due to ACTH. I do not think it is likely, as she apparently was not given ACTH. Cortisone has been put in nose drops; when it is used in cough drops it may be one of the toxic agents we shall have to think about. I think I may also dispose of certain other causes of unconsciousness in which recovery or death ensues immediately, such as ordinary syncope, carotid-sinus attacks and Stokes–Adams syndrome.

Now let me go on to the meaty possibilities. In the first place, a cerebral embolus is a good possibility. It is one of those catastrophes that cause almost immediate unconsciousness. There are certain things about that theory that do not fit well. There was no lateralization. To be sure, lateralization is not necessary as whenever coma is very profound there may be no lateralization at first; even though the cause may be in the central nervous system, lateralization may not appear until late. On the other hand, it is not necessary to assume, because of the nervous-system findings, that the coma originated in the nervous system, since in any situation in which shock is as important as it was in this case there may be nondescript nervous-system findings, which is the category I choose to put these in.

The next possibility I should like to mention is another type of embolus, resulting in pulmonary infarction. I do not believe that pulmonary infarction is ordinarily followed by real unresponsiveness unless death occurs shortly thereafter. If complete unconsciousness ensued as the result of pulmonary infarction, it is most unlikely that the patient would have lived for fourteen hours and then died; I think that either death would have come sooner or she would have shown some responsiveness.

The next category includes disorders of the brain itself, such as subarachnoid hemorrhage, hemorrhage into one of the hemispheres or multiple sclerosis, with which acute episodes of unconsciousness sometimes occur. I think I can dismiss multiple sclerosis, as there was no other evidence for it. There were no cells in the spinal fluid to suggest subarachnoid hemorrhage and no lateralization to indicate a large hemorrhage into the hemisphere. As I have said, this is not completely ruled out by the lack of lateralization because of the depth of coma, but it is unlikely.

Another possibility is a myocardial infarction. Again, it seems unlikely that the patient would have lived fourteen hours after severe myocardial infarction without showing some responsiveness, although it is possible. The evidence — or lack of evidence — in the electrocardiogram is somewhat against a myocardial infarction.

I am left with the possibility that seems most likely; that is, a dissecting aortic aneurysm. I really believe dissecting aneurysm is the diagnosis, because there were certain special little items that fit a dissecting aneurysm and nothing else, whereas the other findings fit a number of possibilities. What are these special little items? In the first place, the observation of pain in the neck the night before admission is rather hard to explain otherwise. It may be explained by meningitis, which she obviously did not have; I shall disregard that possibility. The second point is that the pulses were absent in the right arm; that would go very neatly with dissection of an aortic aneurysm. The third point is the leukocytosis. Although high for a dissecting aneurysm, it is somewhat more consistent with that than with a cerebral embolus, which is the second possibility. The fourth finding of interest is the fact that the neck veins became more markedly distended on the right. That these keen observations were made during a total illness of fourteen hours is exceptional. Neck veins are difficult to observe properly; when the remark is made that they were perfectly flat on entry and distended within fourteen hours, more markedly on the right, it is important. It leads me to believe that the patient came from Dr. Conger Williams' service, inasmuch as he is a great enthusiast for proper observation of neck veins. The

only thing against a dissecting aneurysm is one of the exceptions I raised to certain other diagnoses: that it is a little surprising that she did not recover consciousness prior to death. However, I face either that barrier or lack of lateralization with almost any diagnosis. I shall have to accommodate one of them; I think it is best to accommodate it in terms of a dissecting aneurysm.

DR. DANIEL S. ELLIS: Where would you place the aneurysm?

DR. BERG: It apparently involved both carotid arteries but had not involved the aorta farther on, therefore it presumably had gone that far and no farther. Incidentally, even with a cerebral hemorrhage, which would be the second possibility, one would expect that at least one corneal reflex would be present. The divergent strabismus also would be disturbing with that diagnosis. It would fit much better with a generalized anoxia than with interference farther down, I should think.

CLINICAL DIAGNOSES

Hypertensive cardiovascular disease.
Cerebrovascular accident, ?basilar artery.

DR. BERG'S DIAGNOSIS

Dissecting aneurysm of aorta, involving both carotid arteries.

ANATOMICAL DIAGNOSIS

Ruptured aortic dissecting aneurysm, with occlusion of innominate artery.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: This patient did have a dissecting aneurysm — one unlike any seen previously in this laboratory. The lesion began from an intimal tear in the ascending aorta and extended over the arch and down the descending aorta to a point about 4 cm. above the bifurcation, where there was a rerupture into the lumen of the aorta. The unusual feature was the dissection for a distance of 2 cm. of the innominate artery, which was occluded by bulging of the intima. We have had many cases of dissecting aneurysm in which the dissection extended from the aorta into the iliac artery and produced temporary occlusion of the circulation to one or both legs. This is the first time that we have seen it go so extensively into the innominate artery and produce actual occlusion. There is no anatomic reason that that should not occur much more often, because the innominate artery and other branches of the arch are elastic arteries of the same structure as the aorta, so that they may readily dissect. The terminal event was the usual external rupture of the adventitia of the ascending aorta at the level of the intimal tear into the pericardium.

The examination of the brain showed multiple small areas that were interpreted as embolic or ischemic foci, but there were no occlusions or hemorrhages directly from the cerebral vessels.

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THE FAR VIEWPOINT

If specific instances of ill conduct were to be investigated deeply enough, it might be found that the difficulty in distinguishing between right and wrong is often a greater cause of wrongdoing than downright evil, and that a genuinely receptive mind is the one most capable of making that distinction and benefiting thereby.

The communist-dominated Chinese, for example, may sincerely believe themselves to be potential victims of aggression in Asia, just as the United Nations — some of them faintheartedly — consider themselves the injured parties. It may even be that those who determine the policies of Russia seriously fear the isolation of that confused and desperate nation by the more sophisticated, if still less heavily armed, countries to the west.

Were some safe plateau of mutual understanding to be reached, a morass of unnecessary human misery might be avoided by everyone.

There is little doubt that the more ardent proponents of compulsory health insurance, so called, believe that modified socialism represents a political status that can be maintained, and that those citizens capable of the most intelligent leadership and imbued with the purest motives will automatically rise, like cream, to the top. Their opponents, on the other hand, despite their bitter vehemence, have no good reason for not examining with an open mind any proposals that are made and accepting those that can honestly be said to represent progress toward a common goal.

The unpopular belief that important issues can rarely be decided on a clear-cut basis of right and wrong is still cherished by a small but stubborn group. The choice, as has been declared before (even in these pages), is not between black and white, but between two different shades of gray, the comparative intensity of which may vary according to the observer.

The difficulty for those who wish to be honest is not in deciding whether to follow a right course or a wrong one; it lies in liberating their minds from misconceptions and prejudices, so that they may more accurately decide where the greater good may lie. In doing this, they may realistically appreciate their opponents' reasons for holding to their own views.

Edwin T. Dahlberg, in *Advance* (November, 1950), expresses somewhat similar ideas from an ecclesiastical point of view:

> What sent Christ to the cross was not so much the sin that people knew to be evil and shameful but rather the national ideals that people were convinced were so positively holy. We are betrayed by our ideals more often than we realize; family loyalties, patriotic and religious slogans, political and economic groupings. We surround these ideals with sacred flags, banners and rituals, and before we know it, we are nailing Christ to the cross and the ideals become his crown of thorns.

In this, one of the darkest periods in the slow agony of man's efforts to fit himself to his environment, one well may wonder if his apparent progress

is only that of Sisyphus, laboring eternally with his stone toward the unattainable summit of the hill. Man still must learn that true progress is not made through scientific achievement or the acquisition of knowledge, but through the wise application of their resources.

Hooton[1] put on the line the real facts concerning any biological improvement in man's capacity when he wrote:

> I am acquainted with no anatomical, physiological, psychological, or cultural evidences that indicate that progressive evolution of the human brain and of the human intelligence has continued since the fifth millennium before Christ, when man succeeded in domesticating animals and cultivating plants.

Bertrand Russell, writing in the *British Medical Journal* and quoted by Emerson[2] in his fifty-year progress report on public health, described man's impassé most succinctly: "Unless men increase in wisdom as much as in knowledge, increase in knowledge will be an increase in sorrow."

Salvation for the present race of mankind, if it is to come, will come not through the development of superior qualities, but through the proper use of the talents that man now possesses. It is not his to soar on wings attached with wax, but to stand erect on the good earth he now inhabits. The capacity is present. What is necessary is education, with emphasis on ethics, and a stirring of the loftier minds to assume that leadership without which the goal so nearly won is lost.

REFERENCES

1. Hooton, E. *Man's Poor Relations.* 412 pp. Garden City, New York: Doubleday, Doran & Company, Inc., 1942.
2. Emerson, H. Fifty years of medical progress: medicine as social instrument: public health. *New Eng. J. Med.* 244:289-296, 1951.

"AN INHUMANE BILL"

THE *Boston Post*, in an editorial published on February 23, seems utterly to have missed the point of the Pound Bill that currently went down to defeat in the legislature.

The editorial, entitled "An Inhumane Bill," completely ignored the true meaning of the proposed legislation to the point where one may well wonder if the writer attended the hearing on the bill, or, indeed, had even read it.

It may be useless to repeat certain facts concerning these proposals for ears that will not hear, for eyes that will not see and for minds that will not comprehend. And yet for humanity's sake it is only just that further efforts should be made to convince those who opposed the bill on the ground that personal pets will be sacrificed that such is not the case.

The eventual fate of impounded animals under the legislation that the Post *helped to defeat would be the same as it is under the present law — a merciful execution — unless the waiting period required before their disposal was lengthened — a charge to which the sponsors of the bill were entirely agreeable.*

If the editorial policy of the *Post* is against animal experimentation in the interest of humanity, then let the editors say so, honestly and manfully; otherwise they are urged to acquaint themselves thoroughly with the provisions of such bills before condemning them on grounds that do not exist.

STUDENT AMERICAN MEDICAL ASSOCIATION

ON DECEMBER 28 and 29, 1950, student representatives of forty-eight medical schools convened in Chicago to initiate the organization of a Student American Medical Association. This meeting was held at the invitation of the Board of Trustees of the American Medical Association in response to an expressed desire on the part of medical students for a new national organization to serve their interests.

Each representative took part in the drafting of the constitution, which provides for effective control of the organization by the students themselves while maintaining liaison with the county and state medical societies and an organic relationship to the American Medical Association. Executive authority is vested in an Executive Council of thirteen, made up of ten student councilors who are elected by the House of Delegates of the Student American Medical Association and three senior councilors appointed by the Board of Trustees of the American Medical Association. An executive secretary, who has no vote in the Executive Council, is also appointed by the American Medical Association.

It is noteworthy that in their constitutional convention the students adopted a clause providing that no local "society may refuse membership on the basis of race, religion, color or sex," and at the same time voted down a provision that would require an oath of allegiance for membership.

The local unit is an "academic society" that may be organized by the undergraduates of any approved medical school and must constitute not less than one quarter of the total student body or eighty-five students, whichever is the smaller number: Interns may be admitted at the discretion of the local academic society.

Each academic society has an advisory committee composed of the dean of the medical school or his appointed representative, two faculty representatives elected by the academic society, one representative appointed by the county medical society and one representative appointed by the state medical society. The House of Delegates of the Student American Medical Association elects two members of its Association as its representatives to the House of Delegates of the American Medical Association.

The new society plans to publish a special journal of the Student American Medical Association at some time in the future, under the supervision of the Executive Council. In the meantime, space will be made available in the *Journal of the American Medical Association*.

The new society will give to the American medical student an unprecedented opportunity to make known his needs and aspirations. He may be expected to offer valuable criticisms of the present system of medical education and to give a new viewpoint on many problems that are close to his heart and of which he has special knowledge, such as medical-school admissions policies and internships. At the same time, he will become familiar with the workings of the medical societies at the county, state and national levels and with the role that he as a physician will be expected to play in them. He will thus be equipped — and, we may hope, inspired — to take an active part in the affairs of organized medicine at an earlier age than in the past. May he bring to their councils something of the fresh ideals, the unclouded vision and the bold spirit of youth!

POSTGRADUATE EDUCATION

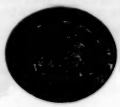
Boston, long one of the world's great centers of undergraduate medical education, with its three high-ranking medical schools and its group of teaching hospitals, is also gaining increased prestige as a focal point of postgraduate instruction. This function has come to be of top priority in the Massachusetts Medical Society as well as in the schools and hospitals.

The course that the Orthopedic Department of the Boston City Hospital is offering next month, in conjunction with Boston University School of Medicine, is noteworthy for its guest speakers, particularly the guest conductor, Dr. Lorenz Böhler, of Vienna. Other visiting lecturers will be Dr. Herbert F. Moseley, of Montreal, Dr. Preston A. Wade, of New York, and Dr. J. Huber Wagner, of Pittsburgh.

Dr. Wm. Wood gives an interesting case, in the London Lancet, of a man, confined in the Bethlem Hospital on account of insanity, who became completely restored to his health and reason, after a tape-worm had been discharged by the administration of that celebrated anthelmintic kousso.

Boston M. & S. J., *March 19, 1851*

MASSACHUSETTS MEDICAL SOCIETY



DEATHS

Page — Calvin G. Page, M.D., of Brookline, died on February 25. He was in his eighty-fourth year.

Dr. Page received his degree from Harvard Medical School in 1894. He was research bacteriologist for the Orthopedic Department of the Children's Hospital and the Ear and Throat departments of the Massachusetts Eye and Ear Infirmary. He was a member of the National Tuberculosis Association, the American Association of Pathologists and Bacteriologists, the Society of American Bacteriologists and the American Public Health Association and a fellow of the American Medical Association.

His widow, two daughters and two grandsons survive.

Thom — Douglas A. Thom, M.D., of Boston, died on February 23. He was in his sixty-fourth year.

Dr. Thom received his degree from the University of Vermont College of Medicine in 1912. He was founder and director of the Boston Habit Clinic for Child Guidance. He was a member of the American Neurological Association, the American Psychiatric Association, the New England Society of Psychiatry and the American Psychopathological Association and a fellow of the American Medical Association.

His widow and a son survive.

BOSTON MEDICAL LIBRARY

SIDE-LINES OF MEDICAL HISTORY

Supplementing any collection on medical history, there are a number of classes of ephemeral material that are important in developing the complete picture of medicine, either locally, nationally, or from an international point of view.

There may be mentioned, in this connection, autograph letters and signatures of physicians. Today, most letters are typewritten and signatures are the best one may expect to receive, unless it is possible to persuade the selected doctor to write a longhand letter for inclusion in a collection. The entire letter should be saved — not the signature alone. It should be remembered that the young doctor of the present time may become the famous physician of the years to come, and that all autographs should be collected.

The Library has a collection of letters and signatures and seeks to add to it either single items or collections. Some years back the late Dr. James A. Spalding of Portland, Maine, presented to the Library a large number of letters of the famous Dr. Lyman Spalding, a pioneer in medicine in New England. Dr. Frederick C. Shattuck of Boston received during his lifetime many letters from eminent physicians throughout the world. He saved these letters and presented them from time to time to the library.

A number of prominent physicians in Boston today are receiving letters of a nonconfidential character from physicians, and it is suggested that these letters be presented to the Library and not destroyed or dead-filed when their usefulness has expired.

During the past few years, interesting letters have been received singly or in lots. The lots included collections of letters of James Thacher, 1781–1842; Ezekiel G. Dodge, 1789–1819; Ezekiel D. Cushing, 1799–1827; Zadok Howe, 1812–1827 and Robert Andrews, 1825–1845 — all of New England and those of Julius Griffiths, 1810–1829, an Englishman.

From Boston there are letters of H. I. Bowditch, V. Y. Bowditch, D. W. Cheever, B. E. Cotting, Edward Cowles, E. G. Cutler, R. H. Fitz, G. W. Gay, Abner Post and J. Collins Warren. From abroad, there are letters from noted physicians: George A. Gibson, William McDougall, D'Arcy Power, Charles S. Sherrington, James Y. Simpson and Max Neuburger, the medical historian.

Unfortunately, the Library has not sufficient personnel to arrange and list the accumulation of this material. Retired physicians who have a few hours, leisure time to spare each week would find such light work an interesting avocation and at the same time contribute a valuable service to the Library.

NOTES FROM THE MEDICAL EXAMINER

MYOCARDITIS OF UNDETERMINED ORIGIN: A CAUSE OF UNEXPECTED DEATH

During the course of two years of autopsy examinations by members of the Department of Legal Medicine at Harvard Medical School, six deaths have been disclosed that were due to what might best be called "myocarditis of undetermined etiology." All cases involved adults in the young and middle-age groups and all died unexpectedly without previously recognized illness. All were presumably in good health and carrying out their usual activities. Gross autopsy examinations showed only nonspecific changes such as edema of the lungs and dilatation of the heart. In only two of the six cases was there found appreciable gross evidence of disease in the myocardium. This consisted of a barely perceptible hemorrhagic mottling in one and a gray mottling suggestive of focal fibrosis in the other. Microscopical examination of the heart muscle in these cases showed varying amounts of inflammatory change. The cases in which there were gross changes showed extensive focal scarring of the myocardium, together with scattered areas of inflammatory exudate consisting mostly of small mononuclear cells with a few neutrophils. The other cases were more interesting, in that only a few of the total number of sections from any one heart showed significant inflammatory change. Only careful scrutiny of routine sections pointed the way to more extensive examination of the heart muscle in these cases. Obviously, the reason for this is that sections of myocardium taken at random may not disclose relatively small foci of inflammation. The foci found were almost invariably small, consisting of collections of lymphocytes with occasional neutrophils. Some lay between muscle bundles; more often they were found about small blood vessels. Sections showing these changes were taken from the interventricular septa as well as from other portions of the left ventricular wall. The inflammatory changes noted were in almost all cases limited to the myocardium, the endocardium not being involved.

None of the cases showed specific gross or histologic changes suggestive of rheumatic myocarditis or endocarditis. However, the histologic changes found in rheumatic involvement of the heart are so variable that it is not possible completely to exclude the disease as an explanation.

The etiology of such inflammatory change must be left to conjecture. Whether or not such lesions are associated with ordinary minor viral infections is an unanswered question. The mechanism of death in these cases of "subclinical myocarditis" is another conjectural matter, although a facile explanation is that there is some disturbance of conduction in the left ventricular muscle provoked by even slight inflammatory changes, leading to ventricular fibrillation and death.

Consideration of this group of cases suggests that perhaps a more detailed microscopical examination of the myocardium in persons dead unexpectedly or suddenly, in whom no adequate cause of death is discovered in a "routine" examination, might be profitable. A certain percentage of cases (ordinarily stated to be 5 per cent) involving sudden or unexpected death actually remain completely unexplained even after extensive post-mortem examination, including toxicologic analysis. The traditional attitude toward these cases ascribes them to obscure physiologic mechanisms without anatomic changes or regards them as instances of inadequate examination. Perhaps fewer cases would fall into this group if more extensive examination of the heart muscle were made.

MICHAEL A. LUONGO, M.D.
Instructor in Legal Medicine
Harvard Medical School
Associate Medical Examiner
Suffolk County

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CLINICS FOR ALCOHOLICS

IT IS the intent of the Department to encourage the establishment of clinics for the treatment of alcoholics on an ambulatory basis in the outpatient departments of general hospitals in suitable locations throughout the Commonwealth. The pattern of organization to be followed will be similar to that of other clinic facilities operated co-operatively by the Department and general hospitals. It is the further intent of the Department that these clinic facilities for alcoholism shall be part of the regular services offered the community by the hospital, and as such the hospital should assume some administrative responsibility for these services.

The outpatient clinic is considered to be the basic unit of service to the alcoholic. In each case the different problems involved must be diagnosed and plans formulated for their treatment. The patient must be helped to adjust his life, without alcohol, to the community or environment wherein he lives or expects to live. Merely to keep the alcoholic sober in the artificial environment of an institution or in complete dependence on a therapist is expensive, ineffective and certain to lead to failure.

Establishment of such clinics in outpatient departments of general hospitals offers many advantages. To the alcoholic, it means the acceptance of his affliction as a disease to be cared for in an institution in which other ailments to which man is heir are similarly treated. This would tend to remove the stigma so frequently attached to alcoholism and render the alcoholic more readily willing to admit his inability to handle alcohol, and to seek help. These are attitudes that are essential to successful therapy. To the physician, it means the availability of specialized diagnostic and therapeutic services necessary for treating the patient as a whole. To the hospital staff, it offers firsthand knowledge of the nature of alcoholism and its treatment. Furthermore, it makes available a facility to which patients primarily admitted or hospitalized for an organic illness may be referred for study and treatment of a secondary alcoholic problem. To the hospital, it means the offering of additional beneficial services to the community and thereby the increasing of its prestige.

Facilities for inpatient care are to be available at the hospital to supplement the work of the clinic. Patients will be admitted only from the clinic upon referral of the physician in charge. These facilities are not intended for purposes of "sobering up" or "drying out" unco-operative and unresponsive alcoholics merely seeking a haven during an alcoholic storm.

CORRESPONDENCE

SERVICE DEFINED

To the Editor: Several of the recent editorials in the *Journal*, particularly "Cold Turkey," in the issue of November 23, give us plenty to think about. You note the results of "The earth's most troublesome biped's having forsaken true values . . ." and you mention the need for "changes in outlook."

Because material wealth in America has made it easy to provide living standards for most people beyond the dreams of our forefathers, we have pointed to our material achievements in pious virtue. Perhaps we forget or never learned that the reformers who demanded better living conditions for the underprivileged a hundred years ago were fired by inner convictions based largely upon religious teachings. That some reformers had no use for organized religion is chiefly evidence that they were dissatisfied with the performance of many self-styled Christians.

Today our way of life is threatened from the outside; but perhaps our righteous indignation at the Communists is to a considerable extent a projection of our own faults upon them. Perhaps the threat from the inside is really bigger. It was pointed out that the man who has "accepted material goals and rewards now imagines himself to be forsaken when he finds that his achievements do not bring satisfaction."

I believe we physicians should spend time each day trying not only to find and define the faith and philosophy we must have to meet our own personal day-to-day problems but also to discover the ways in which we may best serve a universal patient — the ailing world. For Americans, who have freedom as their watchword, a simple faith might be faith in God "whose service is perfect freedom." An expression of service to God might be "Thou shalt love the

Lord thy God with all thy heart and with all thy soul and with all thy mind, and thy neighbor as thyself."

Psychiatrists have rediscovered love as the strongest force binding people together, particularly children and parents. It has been shown that the mentally ill person may find his cure when he can establish a "warm" relationship with another human being, when he can develop and utilize his capacity to love. The emotionally mature person is one who uses his capacity for love in his daily contacts with people. Perhaps it is appropriate to struggle also to love the Power behind life and death. If a man loves God, he must love his neighbor because his neighbor, as a part of the universe, is also a part of God.

If we try all this we shall still lack "perfect freedom," without still another concept. It has been said that to love God and serve Him we must willingly ". . . offer and present [to Him] our selves, our souls and bodies . . ." This may sound idealistic, impractical or even meaningless. It suggests, among other things, that we shall no longer be captain of our ship. Perhaps it deserves consideration in a larger context. We have long since accepted the authority of nature's more obvious laws. So it should be with the law that only those men and women are perfectly free who voluntarily offer their lives daily to a Power beyond themselves. Some of them hardly recognize that this is what happens. But their neighbors sense it even though it is unexpressed. These are not necessarily monks or nuns. They are housewives, businessmen, laborers, doctors and so forth. They are free because they no longer spend half their energies struggling to break the immutable laws.

We need something more for the groups that exist in the world. Just as co-operation and teamwork are fundamental to medical care today, so our spiritual concepts must be worked out in co-operation with others. The Soviet leaders have shown us that organized groups of people holding the same beliefs, working with each other in groups and constantly re-enforcing each others' beliefs, can exert an enormous influence on the course of events. Their spiritual strength derives from their use of the basic drives for solidarity within the group, and the channeling of the drives for hatred and other destructive emotions toward outsiders. Only a small percentage of any population would willingly accept a philosophy of lies and hatred "justified" by atheism. Thus the side of communism that teaches hatred carries the seeds of its own destruction.

But will that destruction be our destruction? Hatred can be conquered by love but not by bullets. We willingly spent billions for arms to preserve our way of life. In the last few years we have also spent billions for the cultural and economic rehabilitation of our neighbors. We hope the latter program is a better definition of our beliefs and intentions. But do we, as doctors, spend time with ourselves, with our families, with our patients, with our colleagues or with the medical students we teach considering the spiritual dangers and trying to define our own beliefs and live up to them? Do we offer our troubled or dying patients any help in finding faith or philosophy? Perhaps one step in doing something about the world's needs that you have discussed editorially would be for all of us physicians to begin the improvement with ourselves.

J. Wister Meigs, M.D.

Hamden, Connecticut

ARRANT PEDANTRY

To the Editor: Professor Salter, in his scholarly article on fifty years of progress in pharmacology, repeats a common misquotation from Oliver Wendell Holmes. This is perhaps excusable, for New Haven is hardly a part of New England any longer, but the Editor of the *New England Journal of Medicine*, working in the building of the Boston Medical Library so intimately associated with Dr. Holmes, should have come to his aid. Dr. Salter quotes: "If the whole Materia Medica (excepting only opium and ether), as now used, could be sunk to the bottom of the sea, it would be all the better for mankind, — and all the worse for the fishes."

A reading of Dr. Holmes' *Medical Essays* would show that he said: "The large exception of *opium, wine, specifics* and *anesthetics*, made in the text, takes off enough from the useful side, as I fully believe, to turn the balance"; Dr. Holmes was always careful in his statements. As Dr. Salter quotes toward the end of his article, "If we want to see ahead we must look back."

Peter Pineo Chase, M.D.

Providence, Rhode Island

Note: Dr. Salter has erred only in his parenthetical and condensed inclusion of some preliminary remarks with which Dr. Holmes introduced the quoted passage, and in a slight laxity in the use of capitals and the omission of italics. The reference is to "Currents and Counter-Currents in Medical Science," an address delivered before the Massachusetts Medical Society at the Annual Meeting, May 30, 1860. It is to be found, as Dr. Chase intimated, in the Boston Medical Library — in the 1891 edition of *Medical Essays*, copyrighted by Oliver Wendell Holmes and published by Houghton, Mifflin Company. The passage is as follows:

> Throw out opium, which the Creator himself seems to prescribe, for we often see the scarlet poppy growing in the cornfields, as if it were foreseen that wherever there is hunger to be fed there must also be pain to be soothed; throw out a few specifics which our art did not discover, and is hardly needed to apply . . .; throw out wine, which is a food, and the vapors which produce the miracle of anaesthesia, and I firmly believe that if the whole materia medica, *as now used*, could be sunk to the bottom of the sea, it would be all the better for mankind, — and all the worse for the fishes.

Dr. Salter and the Editor can afford to be indulgent with their old friend Peter Pineo Chase. Let the Editor of the *Rhode Island Medical Journal* beware, however, before he pushes them too far. — *The Editor.*

BOOK REVIEW

Gynecology: *The teachings of John I. Brewer*. By John I. Brewer, M.D., Ph.D. 8", cloth, 437 pp., with 66 illustrations. New York: Thomas Nelson and Sons, 1950. $7.50.

This volume differs in method from the conventional, standard, systematic textbook in that its author selects seventeen basic symptomatic entities, under which as captions he discusses and reviews the entire field of gynecology. His purpose is twofold: to present the material in the form in which it can best be used in diagnosis, treatment and teaching; and to offer sufficient information for the student to develop an effective pattern of thinking in the examination and treatment of patients. This method inevitably involves occasional repetition, but has the advantage of traversing the subject exactly as it occurs in practice. This unusual work, illustrated with 66 admirable original plates, not only embodies the author's teachings but also reflects those of his teacher, Dr. Harold O. Jones, to whom the volume is dedicated.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Medical Physics. Vol. II. Editor-in-chief, Otto Glasser, Ph.D., professor of biophysics, Frank E. Bunts Educational Institute, head, department of biophysics, Cleveland Clinic Foundation, and consultant, United States Veterans Administration, Washington, D. C. Associate editors: all contributors to Vol. I and II. Editorial assistant: Jessie C. Tucker, Cleveland, Ohio. 4", cloth, 1227 pp., with illustrations. Chicago: Year Book Publishers, Incorporated, 1950. $25.00.

In 1944 the first volume of this comprehensive reference treatise was published. The second volume is not a revision of the first but is designed to supplement and complement it and to bring up to date the literature on the subject. Ninety-five chapters represent new material. Fifty-eight chapters

deal with subjects appearing in the first volume but requiring complete rewriting or substantial revision. In addition there are supplementary discussions of a large number of subjects appearing in the first volume. The new subjects are too many to be listed but comprise topics of important current interest. The set should be in all large medical libraries for reference purposes.

Factors Regulating Blood Pressure: Transactions of the third conference, May 5-6, 1949, New York. Edited by B. W. Zweifach and Ephraim Shorr, Department of Medicine, Cornell University Medical College. 8°, paper, 280 pp., with 48 illustrations and 24 tables. New York: Josiah Macy, Jr., Foundation, 1950. $2.55.

Twenty-seven persons took part in this important conference, discussing various aspects of blood pressure. The series should be in all medical libraries.

You and Your Heart: A clinic for laymen on the heart and circulation. By H. M. Marvin, M.D., T. Duckett Jones, M.D., Irving H. Page, M.D., Irving S. Wright, M.D., and David D. Rutstein, M.D. With a foreword by Paul D. White, M.D. 8°, cloth, 306 pp. New York: Random House, 1950. $3.00.

This popular book on the heart has been written by competent authorities. Dr. White in his foreword states, "never before has there been assembled under one cover for the layman such a wealth of accurate and useful cardiovascular information, written in a clear and simple style." The publishing is excellent, and the book is recommended for all public and medical libraries and to the laity.

Proceedings of Lead Hygiene Conference. Held at Bismarck Hotel, Chicago, Illinois, November 15-16, 1948. 8°, paper, 137 pp., with illustrations and tables. New York: Lead Industries Association, 1950. $1.00.

The proceedings of this special conference consists of 10 principal papers, 4 of which are on various aspects of lead poisoning. There are also papers on aluminum and silicosis, air-pollution regulations and various aspects of lead hygiene in industry. The small book should be in all collections on toxicology and industrial medicine.

NOTICES

ANNOUNCEMENTS

Dr. Timothy Dennehy announces the opening of his office for the practice of surgery at 1074 Centre Street, Newton Centre.

Dr. Robert W. Riemer announces the opening of his office for the practice of surgery at 183 Angell Street, Providence, Rhode Island.

Dr. Francis Rouillard announces the removal of his office to 319 Longwood Avenue, Boston.

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The Boston City Hospital House Officers' Association will present the following lectures, to be given in the Dowling Amphitheatre at 7 p.m., in its evening lecture series.

Tuesday, March 20. Oral Changes Indicative of Systemic Disease. Harold Jeghers, M.D., professor of medicine, Georgetown University School of Medicine.

Tuesday, March 27. Practical Considerations in the Management of Diabetes. Garfield Duncan, M.D., clinical professor of medicine, Jefferson Medical College, and chief of medicine, Pennsylvania Hospital.

Wednesday, March 28. Granulomatous Diseases of Lungs and their Effect on Pulmonary Function. George W. Wright, M.D., director of Physiology Laboratory, Trudeau Foundation.

All interested persons are invited to attend.

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Conference Program
9-10 A.M.

Tuesday, March 20 — Hyperventilation. Dr. David Kaufmann.

Wednesday, March 21 — The Use of Radioactive P.A.S. as a Diagnostic Procedure in Tuberculosis. Dr. Irving Kass.

Friday, March 23 — The Myth of Strict Bed Rest in the Treatment of Heart Failure. Dr. Samuel A. Levine.

Tuesday, March 27 — X-ray Conference. Dr. Alice Ettinger and staff.

Wednesday, March 28 — Blood Vessels in Purpura. Dr. Theodore Spaet.

Friday, March 30 — Experience with a New Heparin-Like Anticoagulant. Dr. William C. Moloney.

Conferences are held in the Pratt Lecture Hall.

All exercises are open to the medical profession.

94TH INFANTRY DIVISION LECTURE

The Medical Units of the 94th (Bay State) Division are sponsoring a series of postgraduate medical lectures. The next lecture will be held in the auditorium of Boston University School of Medicine, 80 East Concord Street, Boston, on Thursday, March 29, at 8 p.m.

Dr. Alexander Burgess, area section chief of medicine, Veterans Administration, regent of the American College of Physicians, and a member of the American Board of Internal Medicine, will speak on the subject "Oxygen Therapy: Physiology and Techniques."

All interested physicians, whether reserve officers or not, are cordially invited to attend this carefully planned program.

SPRINGFIELD HOSPITAL

The educational program of the Springfield Hospital for the month of March is as follows:

Saturday, April 7.

9-10 a.m. Grand Surgical Rounds.
10-11 a.m. Radiology Conference (topic to be announced) in the Staff Conference Room. Dr. John W. Turner.
11 a.m.-12 m. Combined Medical-Surgical Grand Rounds in the Staff Conference Room.

Wednesday, April 11.

12:15 p.m. Psychosomatic-Medicine Conference in the Staff Conference Room on the subject "Psychoneurosis." Dr. Calvert Stein.

Thursday, April 12.

12:15 p.m. Staff Meeting in the Staff Room.

Saturday, April 14.

9-10 a.m. Grand Surgical Rounds.
10-11 a.m. Seminar on Surgical Principles in the Staff Conference Room on the subject "Stomach Surgery." Dr. James V. Scola.
11 a.m.-12 m. Clinicopathological Conference in the Staff Conference Room.

Tuesday, April 17.

8:30 p.m. Guest Speaker Conference in the Staff Conference Room on the subject "Idiopathic Absorption of Bone Involving Scapula, Clavicle, Humerus, Ribs and Dorsal Vertebrae." Dr. L. Whittington Gorham, professor of oncology, Albany Medical College and physician-in-chief, emeritus, Albany Hospital, Albany, New York.

Saturday, April 21.

9-10 a.m. Grand Surgical Rounds.
10-11 a.m. Plastic-Surgery Conference in the Staff Conference Room on the subject "Treatment of Burns." Dr. Joseph M. Baker.
11 a.m.-12 m. Medical-Death Review in the Staff Conference Room.

Wednesday, April 25.

12:15 p.m. Pediatric Conference in the Staff Conference Room on the subject "Congenital Defects in the Newborn." Dr. H. H. Shuman.

Saturday, April 28.

9–10 a.m. Grand Surgical Rounds.

10–11 a.m. Seminar on Surgical Principles in the Staff Conference Room on the subject "Colon Surgery." Dr. Omar T. Pace.

11 a.m.–12 m. Surgical–Death Review in the Staff Conference Room.

INTERNATIONAL COLLEGE OF SURGEONS

The International College of Surgeons will hold a sectional meeting at the Hotel Somerset on Wednesday, March 28. A program has been arranged to include not only progress in general surgery but also recent advances in the surgical specialties.

The chairman, M. Leopold Brodny, M.D., of 636 Beacon Street, Boston, is in charge of registration.

TUFTS MEDICAL ALUMNI ASSOCIATION

The Tufts Medical Alumni Association will hold its annual dinner meeting on Wednesday evening, April 11, at the Somerset Hotel, Boston.

The guest speaker is to be Mr. Erwin D. Canham, L.H.D., editor-in-chief of the *Christian Science Monitor*, who will discuss "These Great Times."

President Leonard Carmichael of Tufts College will speak on "Who Should Pay for Medical Education?" Dr. Norman Welch, of Boston, will speak as the representative of the twenty-fifth-year reunion class. Dr. Frank R. Ober, president of the Tufts Medical Alumni Association, will preside.

The twenty-fifth-year class will hold its reunion also on this date.

Preceding the dinner there will be open house at the new Medical School building from 1 to 4 p.m.

FELLOWSHIPS IN INFANTILE PARALYSIS

The National Foundation for Infantile Paralysis announces the availability of a number of predoctoral fellowships, covering a period of one year, and postdoctoral fellowships, covering a period of from one to three years, to candidates whose interests are in research and teaching in the fields related to the problems of poliomyelitis, such as virology, biochemistry, biophysics, orthopedics, pediatrics, neurology and epidemiology.

Complete information regarding these fellowships and applications may be obtained from the Division of Professional Education, National Foundation for Infantile Paralysis, 120 Broadway, New York 5, N.Y.

AMERICAN ORTHOPAEDIC ASSOCIATION

The annual meeting of the American Orthopaedic Association will be held at The Greenbrier, White Sulphur Springs, West Virginia, from June 20 to 23.

ARMY NEEDS LINGUISTS

The Office of the Surgeon General, United States Army, has several civilian positions available for medically trained personnel who can read foreign languages, to compile information from foreign medical and other literature. Applicants must be American citizens. Those interested should communicate with the Office of the Surgeon General, United States Army, Attention: Civilian Personnel Branch, Washington 25, D. C.

INTERNATIONAL SOCIETY OF ORTHOPAEDIC AND TRAUMATIC SURGERY

The fifth congress of the International Society of Orthopaedic and Traumatic Surgery will be held in Stockholm, Sweden, from May 21 to 25. The secretary of the Congress is Dr. Anders Karlen, Karolinska Institutets Ortopediska Klinic, Stockholm.

The two main subjects will be "Avitaminosis and Bone Changes," with Dr. R. Zanoli, of Italy, and Dr. E. Rutishauser, of Switzerland, as the principal speakers; and "Low-Back Pain and Sciatica: Results of treatment," with Dr. Joseph S. Barr, of Boston, as the first speaker. In addition, a large number of miscellaneous papers will be presented.

SOCIETY MEETINGS AND CONFERENCES

March 19. New England Cardiovascular Society. Page 384, issue of March 8.

March 20. Harvard Medical Society. Page 346, issue of March 1.

March 20. South End Medical Club. Page 346, issue of March 1.

March 20. Boston City Hospital House Officers' Association. Page 421.

March 20–30. Joseph H. Pratt Diagnostic Hospital. Page 421.

March 21. Phi Delta Epsilon Fraternity Sigma Chapter. Page 346, issue of March 1.

March 21. A Demonstration of Pilot Wearers of Some of the Newer Devices in Prostheses. Dr. Augustus Thorndike. New England Society of Physical Medicine. Hotel Kenmore. 8 p.m.

March 21. Greater Boston Medical Society. Page 384, issue of March 8.

March 22. Hyman Morrison Lecture. Page 74, issue of January 11.

March 26. Boston Lying-in Hospital Obstetric Round-Table Conference. Page 629, issue of October 19.

March 26–28. American Academy of Pediatrics. Page 274, issue of February 15.

March 27. Norfolk District Medical Society. Page 629, issue of October 19.

March 27 and 28. Boston City Hospital House Officers' Association. Page 421.

March 28. International College of Surgeons. Notice above.

March 28. Naval Reserve Volunteer Medical Unit No. 1-1. Page 384, issue of March 8.

March 29. 94th Infantry Division Lecture. Notice above.

April 4. New England Pediatric Society. Page 346, issue of March 1.

April 7. Massachusetts Society of Anesthesiologists. Page 346, issue of March 1.

April 7–28. Springfield Hospital. Page 421.

April 9–13. American College of Physicians. Page 296, issue of June 15.

April 10. New England Society of Anesthesiologists. Page 512, issue of September 28.

April 11. Tufts Medical Alumni Association. Notice above.

April 12. The Diagnosis and Treatment of Kidney Diseases in Childhood. Dr. Charles A. Janeway. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

April 18. Physical Medicine and Rehabilitation in Psychiatry. Dr. Walter E. Barton. New England Society of Physical Medicine. Hotel Kenmore. 8 p.m.

April 24. Norfolk District Medical Society. Page 629, issue of October 19.

April 28. American Psychosomatic Society. Page 198, issue of February 1.

May 7–11. National League of Nursing Education. Page 384, issue of March 8.

May 8. New England Society of Anesthesiologists. Page 512, issue of September 28.

May 9. Norfolk District Medical Society. Page 629, issue of October 19.

May 16. New England Obstetrical and Gynecological Society. Hillcrest Country Club, Leicester, Massachusetts.

May 16–18. American Association of Genito-Urinary Surgeons. Page 160, issue of July 25.

May 21–25. International Society of Orthopaedic and Traumatic Surgery. Notice above.

May 22–24. Massachusetts Medical Society. Annual meeting. Hotel Statler, Boston.

May 24–26. American Goiter Association. Page 384, issue of March 8.

June 9 and 10. American Society for the Study of Sterility. Page 274, issue of February 15.

June 11–15. American Medical Association Annual Session. Atlantic City, New Jersey.

June 15–17. American Electroencephalographic Society. Page 346, issue of March 1.

June 20–23. American Orthopaedic Association. Notice above.

September 4–8. American Congress of Physical Medicine. Page 238, issue of February 8.

September 19. American Medical Writers' Association. Page 1066, issue of December 28.

September 19–21. Mississippi Valley Medical Society. Page 1066, issue of December 28.

October 31. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

November 10–21. Pan-Pacific Surgical Association. Page 680, issue of October 26.

July 8–11, 1952. Thirteenth British Congress of Obstetrics and Gynaecology. Page xv, issue of December 14.

District Medical Societies

HAMPSHIRE

May 2. 4:30 p.m. Annual meeting. Jones Library, Amherst.

NORFOLK

March 27.

April 24.

May 9. Annual dinner.

All meetings except the annual dinner will be held at the Boston Medical Library, 8 Fenway, at 8:00 p.m.

Calendar of Boston District for the Week Beginning Thursday, March 22

Thursday, March 22

*9:00–10:00 a.m. Grand rounds. Robert Breck Brigham Hospital.

*9:00–10:00 a.m. Grand rounds. House of the Good Samaritan.

*9:00–11:00 a.m. Medical grand rounds. Joseph H. Pratt Diagnostic Hospital.

(*Notices concluded on page xvii*)